(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 September 2001 (27.09.2001)

PCT

(10) International Publication Number
WO 01/70743 A1

(51) International Patent Classification[7]: C07D 471/04, 209/08, 209/12, 487/04, A61K 31/437, 31/519, A61P 7/00

(21) International Application Number: PCT/US01/08839

(22) International Filing Date: 20 March 2001 (20.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/190,731 20 March 2000 (20.03.2000) US

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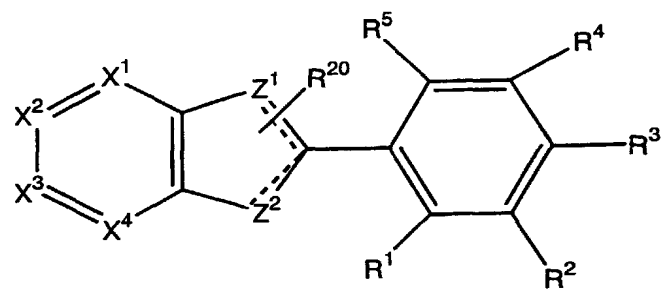
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NON-AMIDINE CONTAINING PROTEASE INHIBITORS



(I)

(57) Abstract: The present invention provides novel compounds of the Formula (I) its prodrug forms, or pharmaceutically acceptable salts thereof. Preferred compounds of the present invention comprise a pyrrolo pyridinyl, pyrrolo pyrimidinyl or indole nucleus. The compounds of this invention are inhibitors of Factor Xa (FXa), Factor VIIa (FVIIa) and/or serine proteases, Urokinase (uPA), and have utility as anti-coagulants for the treatment or prevention of thromboembolic disorders in mammals and as anticancer agents.

WO 01/70743 A1

NON-AMIDINE CONTAINING PROTEASE INHIBITORS

FIELD OF INVENTION

The present invention relates to non-amidine containing novel protease inhibitors.

BACKGROUND OF THE INVENTION

Factor Xa (herein after "FXa"), the converting enzyme of pro-thrombin to thrombin, has emerged as an alternative (to thrombin) target for drug discovery for thromboembolic disorders. A variety of compounds have been developed as potential FXa inhibitors.

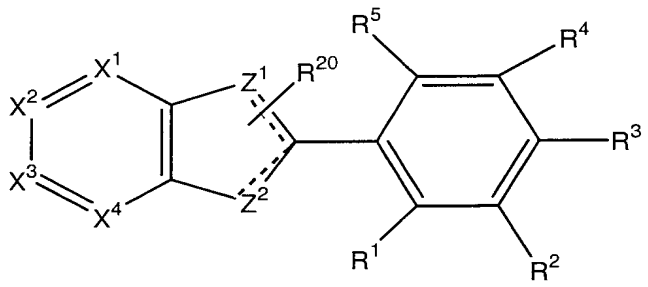
Kunitada and Nagahara in Current Pharmaceutical Design, 1996, Vol. 2, No.5, report amidinobenzyl compounds as FXa and thrombin inhibitors. Disclosed in U.S. Patent No. 5,576,343 are aromatic amidine derivatives and salts thereof, as reversible inhibitors of FXa. These compounds comprise amidino substituted indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazoyl, benzothiazolyl, naphthyl, tetrahydronaphthyl and indanyl groups, attached to a substituted phenyl ring by an alkylene group having from 1 to 4 carbon atoms.

Inhibitors of blood-clotting enzymes such as Factor Xa and Factor VIIa, are also known to be inhibitors of serine proteases such as Urokinase (uPA). Urokinase-type plasminogen activator (uPA) is one class of protease that plays a significant role in the progression of cancer. Inhibitors of uPA have been postulated to be of therapeutic value in treating cancer.

In spite of the above discussed efforts, desirable treatment of cancer and thromboembolic disorders still remains elusive. There is thus a need for new compounds that will be effective in inhibiting blood-clotting enzymes such as FXa and serine proteases, such as Urokinase. Keeping these needs in mind, the present invention provides novel inhibitors as discussed below.

SUMMARY OF THE INVENTION

Keeping the above discussed needs in mind, the present invention provides compounds of Formula I:

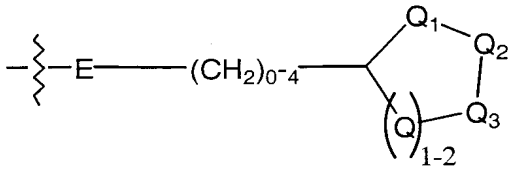


Formula I

its prodrug forms, or pharmaceutically acceptable salts thereof, wherein

R^1 represents OH, halogen, COOH, $COO-C_{1-4}$ alkyl, $O-(CH_2)_{0-1}-Ar$, $N(R^{10})_2$, CH_2OR^{10}, C_{1-6} halogenated alkyl, $O-(CH_2)_{1-4}-CO-N(R^{10})_2$, SC_{1-4} alkyl, $NHSO_2C_{1-4}$alkyl, SO_2-OH, $O-SO_2-OH$, $O-C_{1-4}$ alkyl, $O-C_{3-9}$ cyclo alkyl, $O-SO_2-O-C_{1-4}$ alkyl, $OP(O)(OH)_2$, or OPO_3C_{1-4} alkyl;

R^2, R^3, R^4, and R^5 independently at each occurance represent H, SH, OR^{10}, halogen, $COOR^{10}$, $(CH_2)_{0-6}-CONR^{11}R^{12}$, optionally substituted aryl, optionally substituted heterocyclyl, C_{4-14} cycloalkyl-C_{1-4} alkyl, C_{1-4} alkyl aryl, optionally substituted C_{1-14} straight chain, branched or cyclo alkyl, $O-(CH_2)_{2-6}-NR^{10}-(CH_2)_{0-3}-R^{24}$, $NR^{10}R^{24}$, $(CH_2)_{1-6}-NR^{33}R^{34}$, $(CH_2)_{1-6}-COOR^{33}$, $O-(CH_2)_{1-3}-CO-$het, $O-(CH_2)_{1-2}-NH-CO-$aryl, $O-(CH_2)_{1-2}-NR^{10}-CO-NR^{10}R^{33}$, $(CH_2)_{1-4}-CONR^{10}(CH_2)_{1-4}-$heterocyclyl, $O-(CH_2)_{0-2}-C(O)-NR^{33}R^{34}$, $O-(CH_2)_{1-4}-COOR^{10}$, $O-(CH_2)_{1-3}-$het-R^{32}, O-optionally substituted cycloalkyl, $O-(CH_2)_{1-4}-NR^{10}-COO-t$-butyl, $O-(CH_2)_{1-4}-NR^{10}R^{33}$, $O-(CH_2)_{1-4}-NR^{10}-C(O)-C_{0-3}$-alkyl-optionally substituted aryl, O-substituted cycloalkyl, $O-(CH_2)_{0-6}$-optionally substituted aryl, $(CH_2)_{1-4}-NH-C(O)O-(CH_2)_{1-4}-PhR^{13}R^{14}$, NO_2, $O-(CH_2)_{0-4}-C(O)-NH-$tetrahydro carboline, $NR^{10}R^{28}$, $O-(CH_2)_{1-3}-$optionally substituted het, CH_2COOCH_3, $CH=CH-COOCH_3$, 5-amidino benzimidazole, $SO_2-N(R^{10})_2$,



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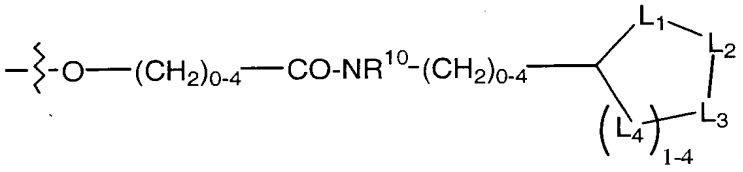

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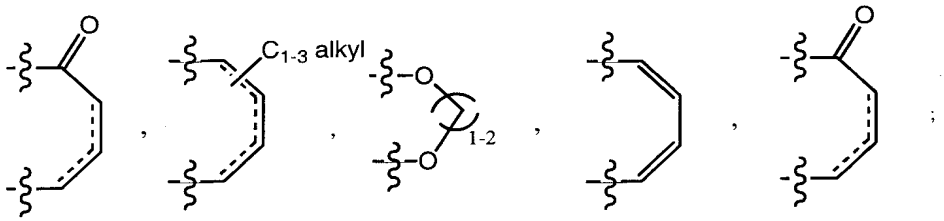
alternatively R^2 and R^3, R^3 and R^4 or R^4 and R^5 can be taken together to form



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X^1 represents C-R^6, N or N-O;
X^2 represents C-R^7, N or N-O;
X^3 represents C-R^8, N or N-O;
X^4 represents C-R^9, N or N-O;
Z^1 and Z^2 independently at each occurance represent C or N;
R^6, R^8 and R^9 independently at each occurance represents H, halogen, cyano, C_{1-4} alkyl, C_{1-4} halogenated alkyl, NO_2, O-aryl or OR^{11}, CF_3, OC_{1-4} alkyl, $(CH_2)_{0-4}$-aryl, $(CH_2)_{0-4}$-heteroaryl, or $(CH_2)_{0-4}$-heterocyclyl;
R^7 represents NH_2, NHR^{10}, $N(R^{10})_2$, $NHSO_2$-C_{1-14} alkyl, NHSO-aryl, OH, NHCO-C_{1-14} alkyl, $NHNH_2$, NHOH, NHCO-C_{1-14} alkyl, $NR^{10}NH_2$, $NHN(R^{10})_2$, $NH(C=NH)NH_2$, $NH(C=O)N(R^{10})_2$; alternatively
R^6 and R^7, R^7 and R^8, R^8 and R^9, along with the respective carbon atoms to which they are attached, can be taken together to represent a 5 to 10 atom saturated, partially saturated or aromatic, carbocyclic or heterocyclic ring structure substituted with R^{41};
R^{10} independently at each occurance represents H, $(CH_2)_{0-2}$-aryl, C_{1-4} halo alkyl, or C_{1-14} straight chain, branched or cyclo alkyl, and alternatively, when one atom is substituted with

two R^{10} groups, the atom along with the R^{10} groups can form a five to 10 cycloalkyl, heterocyclyl or aryl group;

R^{11} and R^{12} independently at each occurance represent H or C_{1-4} alkyl, $(CH_2)_{1-4}$-OH, $(CH_2)_{1-4}$-OC_{1-4}alkyl, $(CH_2)_{0-4}$-aryl, $(CH_2)_{1-4}$-$(R^{10})_2$;

R^{20} represents R^{24}, C_{1-4}-alkyl, $(CH_2)_{1-3}$-biphenyl, $(CH_2)_{1-4}$-Ph-$N(SO_2-C_{1-2}$-alkyl$)_2$, $(CH_2)_{1-4}$-NH-C(O)-R^{24}, $(CH_2)_{1-4}$-NH-SO_2-R^{24}, halogen, $COOR^{10}$, $(CH_2)_{1-4}$-Ph-$N(SO_2-C_{1-2}$alkyl), $(CH_2)_{1-4}$-NR^{10}-C(O)-R^{24}, $(CH_2)_{1-4}$-NR^{10}-SO_2-R^{24}, $(CH_2)_{1-4}$-het, $(CH_2)_{1-4}$-$CON(R^{10})_2$, $(CH_2)_{1-4}$-$N(R^{10})$-C(O)-$NR^{10}R^{24}$, $(CH_2)_{1-4}$-$N(R^{10})$-C(S)-$NR^{10}R^{24}$, or $(CH_2)_{1-3}$-COOH;

R^{24} represents R^{10}, $(CH_2)_{1-4}$-optionally substituted aryl, $(CH_2)_{0-4}OR^{10}$, CO-$(CH_2)_{1-2}$-$N(R^{10})_2$, $CO(CH_2)_{1-4}$-OR^{10}, $(CH_2)_{1-4}$-$COOR^{10}$, $(CH_2)_{0-4}$-$N(R^{10})_2$, SO_2R^{10}, COR^{10}, $CON(R^{10})_2$, $(CH_2)_{0-4}$-aryl-$COOR^{10}$, $(CH_2)_{0-4}$-aryl-$N(R^{10})_2$, or $(CH_2)_{1-4}$-het-aryl;

R^{28} represents $(CH_2)_{1-2}$-Ph-O-$(CH_2)_{0-2}$-het-R^{30}, C(O)-het, CH_2-Ph-CH_2-het-$(R^{30})_{1-3}$; $(CH_2)_{1-4}$-cyclohexyl-R^{31}, CH_2-Ph-O-Ph-$(R^{30})_{1-2}$, CH_2-(CH_2OH)-het-R^{30}, CH_2-Ph-O-cycloalkyl-R^{31}, CH_2-het-C(O)-CH_2-het-R^{30}, or CH_2-Ph-O-(CH_2)-O-het-R^{30};

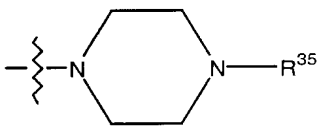
R^{30} represents $SO_2N(R^{10})_2$, H, NHOH, amidino, or $C(=NH)CH_3$;

R^{31} represents R^{30}, amino-amidino, NH-$C(=NH)CH_3$ or R^{10};

R^{32} represents H, C(O)-CH_2-NH_2, or C(O)-$CH(CH(CH_3)_2)$-NH_2;

R^{33} and R^{34} independently at each occurance represent R^{10}, $(CH_2)_{0-4}$-Ar, optionally substituted aryl, $(CH_2)_{0-4}$ optionally substituted heteroaryl, $(CH_2)_{1-4}$-CN, $(CH_2)_{1-4}$-$N(R^{10})_2$, $(CH_2)_{1-4}$-OH, $(CH_2)_{1-4}$-SO_2-$N(R^{10})_2$;

alternatively, R^{33} and R^{34} along with the nitrogen atom that they are attached to forms a 4 to 14 atom ring structure selected from tetrahydro-1H-carboline; 6,7-Dialkoxyoxy-2-substituted 1,2,3,4-tetrahydro-isoquinoline,



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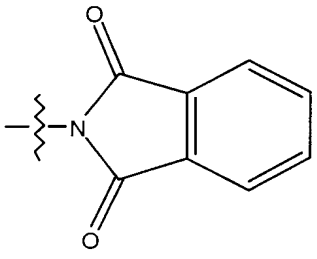


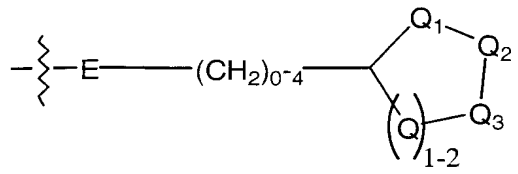
;

R^{35} represents R^{10}, SO_2-R^{10}, COR^{10}, or $CONHR^{10}$;

E represents a bond, $S(O)_{0-2}$, O or NR^{10};
Q, Q^1, Q^2, Q^3, L^1, L^2, L^3 and L^4 independently at each occurance represent N-natural or unnatural amino acid side chain, CHR^{10}, O, NH, $S(O)_{0-2}$, $N-C(O)-NHR^{10}$, $SO_2-N(R^{10})_2$, $N-C(O)-NH-(CH_2)_{1-4}-R^{26}$, NR^{10}, N-heteroaryl, $N-C(=NH)-NHR^{10}$, or $N-C(=NH)C_{1-4}$ alkyl;
R^{26} represents OH, NH_2, or SH;
R^{41} represents NH_2, NHR^{10}, or $N(R^{10})_2$, $NHNH_2$, NHOH, $NR^{10}NH_2$, $NHN(R^{10})_2$, $NH(C=NH)NH_2$, $NH(C=O)N(R^{10})_2$;
provided that, (i) not all of X^1, X^2, X^3 and X^4 represent N or N-O simultaneously.

DETAILED DESCRIPTION OF THE INVENTION

Preferred embodiments of the present invention provide compounds of Formula I, wherein
R^1 represents OH, halogen or COOH;
R^2, R^3, R^4, and R^5 independently at each occurance represent H, SH, OR^{10}, halogen, $COOR^{10}$, $(CH_2)_{0-4}-CONR^{11}R^{12}$, optionally substituted aryl, optionally substituted heterocyclyl, C_{4-14} cycloalkyl-C_{1-4} alkyl, C_{1-4} alkyl aryl, optionally substituted C_{1-14} straight chain, branched or cyclo alkyl, $O-(CH_2)_{2-6}-NR^{10}-(CH_2)_{0-3}-R^{24}$, $NR^{10}R^{24}$, $(CH_2)_{1-4}-NR^{33}R^{34}$, $(CH_2)_{1-4}-COOR^{33}$, $O-(CH_2)_{1-3}-CO-het$, $O-(CH_2)_{1-2}-NH-CO-aryl$, $O-(CH_2)_{1-2}-NR^{10}-CO-NR^{10}R^{33}$, $O-(CH_2)_{0-2}-C(O)-NR^{33}R^{34}$, $O-(CH_2)_{1-4}-COOR^{10}$, $O-(CH_2)_{1-3}-het-R^{32}$, O-optionally substituted cycloalkyl, $O-(CH_2)_{1-4}-NR^{10}-COO-t$-butyl, $O-(CH_2)_{1-4}-NR^{10}R^{33}$, $O-(CH_2)_{1-4}-NR^{10}-C(O)-C_{0-3}$-alkyl-optionally substituted aryl, O-substituted cycloalkyl, $O-(CH_2)_{0-6}$-optionally substituted aryl, $(CH_2)_{1-4}-NH-C(O)O-(CH_2)_{1-4}-PhR^{13}R^{14}$, NO_2, $O-(CH_2)_{0-4}-C(O)-NH-$tetrahydro carboline, $NR^{10}R^{28}$, $O-(CH_2)_{1-3}-$optionally substituted het, CH_2COOCH_3, $CH=CH-COOCH_3$, 5-amidino benzimidazole,



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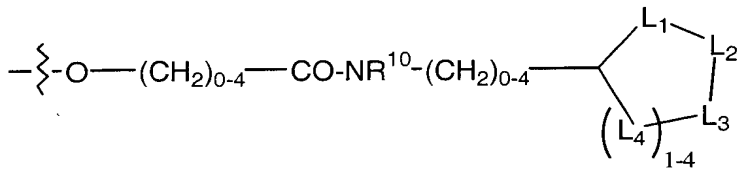

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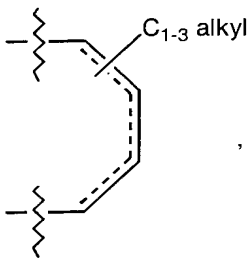
alternatively R^2 and R^3 taken together form



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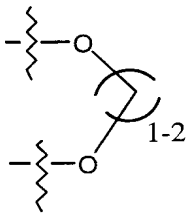

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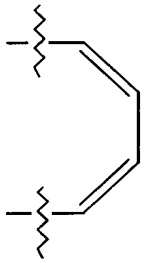


;

X^1 represents C-R^6, N or N-O;

X^2 represents C-R^7;

X^3 represents C-R^8;

X^4 represents C-R^9;

Z^1 represents C;

Z^2 represents N;

R^6, R^8 and R^9 independently at each occurance represents H, halogen, cyano, C_{1-4} alkyl, C_{1-4} halogenated alkyl, NO_2, O-aryl or OR^{11};

R^7 represents NH_2, NHR^{10}, $N(R^{10})_2$, $NHSO_2$-C_{1-14} alkyl, NHSO-aryl, OH, NHCO-C_{1-14} alkyl, $NHNH_2$, NHOH, NHCO-C_{1-14} alkyl, $NR^{10}NH_2$, $NHN(R^{10})_2$, $NH(C=NH)NH_2$, $NH(C=O)N(R^{10})_2$; alternatively

R^6 and R^7, R^7 and R^8, R^8 and R^9, along with the respective carbon atoms to which they are attached, can be taken together to represent a 6 saturated or aromatic, carbocyclic or heterocyclic ring structure substituted with R^{41};

R^{20} represents R^{24}, C_{1-4}-alkyl, $(CH_2)_{1-3}$-biphenyl, $(CH_2)_{1-4}$-Ph-$N(SO_2$-C_{1-2}-alkyl$)_2$, $(CH_2)_{1-4}$-NH-C(O)-R^{24}, $(CH_2)_{1-4}$-NH-SO_2-R^{24}, halogen, $COOR^{10}$, $(CH_2)_{1-4}$-Ph-$N(SO_2$-C_{1-2}alkyl), $(CH_2)_{1-4}$-NR^{10}-C(O)-R^{24}, $(CH_2)_{1-4}$-NR^{10}-SO_2-R^{24}, $(CH_2)_{1-4}$-het, $(CH_2)_{1-4}$-$CON(R^{10})_2$, $(CH_2)_{1-4}$-$N(R^{10})$-C(O)-$NR^{10}R^{24}$, $(CH_2)_{1-4}$-$N(R^{10})$-C(S)-$NR^{10}R^{24}$, or $(CH_2)_{1-3}$-COOH;

R^{24} represents R^{10}, $(CH_2)_{1-4}$-optionally substituted aryl, $(CH_2)_{0-4}OR^{10}$, $CO-(CH_2)_{1-2}-N(R^{10})_2$, $CO(CH_2)_{1-4}-OR^{10}$, $(CH_2)_{1-4}-COOR^{10}$, $(CH_2)_{0-4}-N(R^{10})_2$, SO_2R^{10}, COR^{10}, $CON(R^{10})_2$, $(CH_2)_{0-4}$-aryl-$COOR^{10}$, $(CH_2)_{0-4}$-aryl-$N(R^{10})_2$, or $(CH_2)_{1-4}$-het-aryl;

R^{28} represents $(CH_2)_{1-2}$-Ph-O-$(CH_2)_{0-2}$-het-R^{30}, C(O)-het, CH_2-Ph-CH_2-het-$(R^{30})_{1-3}$; $(CH_2)_{1-4}$-cyclohexyl-R^{31}, CH_2-Ph-O-Ph-$(R^{30})_{1-2}$, CH_2-(CH_2OH)-het-R^{30}, CH_2-Ph-O-cycloalkyl-R^{31}, CH_2-het-C(O)-CH_2-het-R^{30}, or CH_2-Ph-O-(CH_2)-O-het-R^{30};

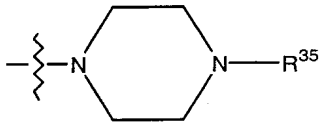
R^{30} represents $SO_2N(R^{10})_2$, H, NHOH, amidino, or $C(=NH)CH_3$;

R^{31} represents R^{30}, amino-amidino, NH-$C(=NH)CH_3$ or R^{10};

R^{32} represents H, C(O)-CH_2-NH_2, or C(O)-$CH(CH(CH_3)_2)$-NH_2;

R^{33} and R^{34} independently at each occurance represent R^{10}, $(CH_2)_{0-4}$-Ar, optionally substituted aryl, $(CH_2)_{0-4}$ optionally substituted heteroaryl, $(CH_2)_{1-4}$-CN, $(CH_2)_{1-4}$-$N(R^{10})_2$, $(CH_2)_{1-4}$-OH, $(CH_2)_{1-4}$-SO_2-$N(R^{10})_2$;

alternatively, R^{33} and R^{34} along with the nitrogen atom that they are attached to forms a 4 to 14 atom ring structure selected from tetrahydro-1H-carboline; 6,7-Dialkoxyoxy-2-substituted 1,2,3,4-tetrahydro-isoquinoline,



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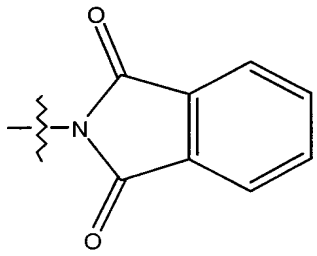

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R^{35} represents R^{10}, SO_2-R^{10}, COR^{10}, or $CONHR^{10}$;

E represents a bond, $S(O)_{0-2}$, O or NR^{10};

W_1, W_2, W_3 and W_4 independently represent C or N; and

Q, Q^1, Q^2, Q^3, L^1, L^2, L^3 and L^4 independently at each occurance represent N-natural or unnatural amino acid side chain, CHR^{10}, O, NH, $S(O)_{0-2}$, N-C(O)-NHR^{10}, SO_2-$N(R^{10})_2$, N-C(O)-NH-$(CH_2)_{1-4}$-R^{26}, NR^{10}, N-heteroaryl, N-$C(=NH)$-NHR^{10}, or N-$C(=NH)C_{1-4}$ alkyl;

R^{26} represents OH, NH_2, or SH; and

provided that, (i) not all of X^1, X^2, X^3 and X^4 represent N or N-O simultaneously.

Provided in yet another preferred embodiment is a compound of Formula I, wherein

R^1 represents OH, O-Ph, COOH, or $P(O)(OH)_2$;

R^2 represents H, halo, optionally substituted alkyl or optionally substituted aryl or heteroaryl;

R^3 represents C_{0-6} alkyl-COOH;

R^5 represents H, C_{1-4} alkyl or OR^{10};

X^1 represents N or N-O;

R^7 represents NH_2 or NHC_{1-3} alkyl;

R^{20} represents H, C_{1-2} alkyl, $(CH_2)_{1-4}$-optionally substituted aryl, $(CH_2)_{1-4}$-het; $(CH_2)_{1-4}$-$N(R^{10})_2$, $(CH_2)_{1-4}$-$CON(R^{10})_2$, $(CH_2)_{1-4}$-NR^{10}-$C(O)$-R^{24}, $(CH_2)_{1-4}$-NR^{10}-SO_2-R^{24}, or $(CH_2)_{1-3}$-COOH.

Another embodiment of the present invention provides compounds of Formula I wherein, X^1 represents C-R^6; X^2 represents C-R^7; X^3 represents N or N-O; X^4 represents C-R^9; Z^1 represents C; and Z^2 represents N. Further preferred compounds are those wherein, R^1 represents OH, COOH, or $P(O)(OH)_2$; R^2 represents H, halo, optionally substituted alkyl or optionally substituted aryl or heteroaryl; R^3 represents C_{0-6} alkyl-COOH; R^5 represents H, C_{1-4} alkyl or OR^{10}; X^1 represents N or N-O; R^7 represents NH_2 or NHC_{1-3} alkyl; R^{20} represents H, C_{1-2} alkyl, $(CH_2)_{1-4}$-optionally substituted aryl, $(CH_2)_{1-4}$-het; $(CH_2)_{1-4}$-$N(R^{10})_2$, $(CH_2)_{1-4}$-$CON(R^{10})_2$, $(CH_2)_{1-4}$-NR^{10}-$C(O)$-R^{24}, $(CH_2)_{1-4}$-NR^{10}-SO_2-R^{24}, or $(CH_2)_{1-3}$-COOH.

Further preferred compounds of Formula I are those wherein, R^1 represents OH or COOH; R^4 represents $(CH_2)_{0-6}$-$COOR^{10}$, optionally substituted heteroaryl, $(CH_2)_{0-4}$-$CONR^{10}R^{11}$, C_{1-10}-straight chain alkyl, branched alkyl or cycloalkyl group substituted with 1-3 groups selected from $COOR^{10}$, $CONHR^{10}$, OR^{10}, or aryl; and R^7 represents NH_2. Yet further preferred compounds of Formula I are those wherein R^1 represents OH;

R^2 represents H, halogen, OH, phenyl, heteroaryl or substituted phenyl; R^4 represents H, halo, $(CH_2)_{0-4}$-$COOR^{10}$, $(CH_2)_{0-4}$-$CONH_2$, $(CH_2)_{0-4}$-$CONHR^{33}$, $(CH_2)_{0-4}$-heteroaryl, C_{1-8} branched alkylene-$COOR^{10}$, or C_{2-6} alkenelyne-$COOR^{10}$; and R^{20} represents H or $(CH_2)_{0-3}$-optionally substituted phenyl, $(CH_2)_{0-3}$-aryl or $(CH_2)_{0-3}$-heteroaryl.

Specifically preferred compounds of Formula i provided by the present invention are:
[3-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-acetic acid ethyl ester;
8-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-bromo-7-hydroxy-3,4-dihydro-2H-naphthalen-1-one;
3-[3-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-propionic acid;
[5-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-acetic acid;
[3-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-acetic acid;
2-[3-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-acetamide;
2-[3-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-N-(2-morpholin-4-yl-ethyl)-acetamide;
2-(5-Amino-1H-pyrrolo[2,3-c]pyridin-2-yl)-4,6-dichloro-phenol;
8-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-bromo-7-hydroxy-3,4-dihydro-2H-naphthalen
-1-one;
3-[3-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-propionic acid;
[5-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-acetic acid;
[3-(5-Amino-1H-pyrrolo[3,2-b]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-acetic acid;
[5-(5-Amino-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-acetic acid;
2-[5-(5-Amino-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-N-(2-morpholin-
4-yl-ethyl)-acetamide;
2-[5-(5-Amino-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-N-(2-methoxy-et
hyl)-acetamide; and
2-[5-(5-Amino-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-N-(2-dimethylamino-ethyl)-acetamide.

Provided in yet another aspect of the present invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. Yet another aspect of the present invention provides a method for treating or preventing a thromboembolic disorder, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to Claim 2 or a pharmaceutically acceptable salt thereof.

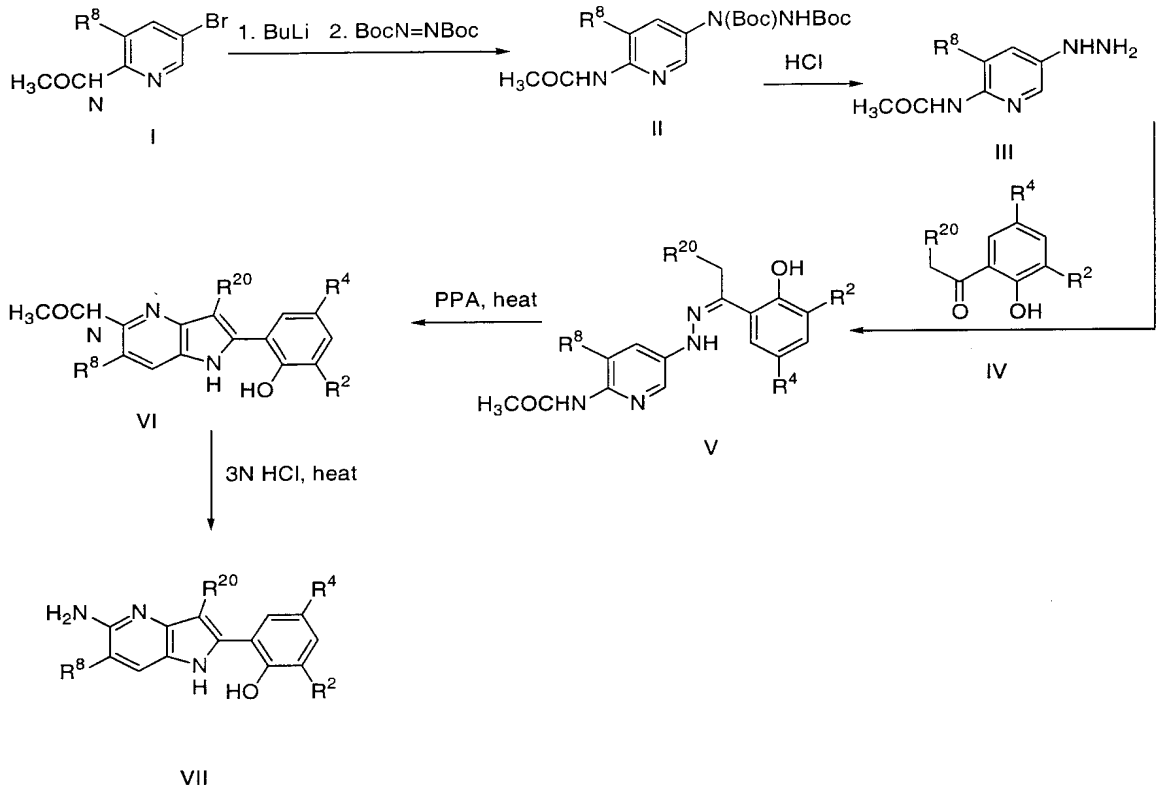
EXPERIMENTAL

Novel compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. Described herein are some of the preferred synthetic methods for synthesizing novel compounds of the present invention. All temperatures reported herein are in degrees Celsius, unless indicated otherwise.

The novel compounds of Formula I can be prepared using the reactions and synthetic techniques described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

Proton NMR's (^{1}H NMR) were obtained using deuterated solvents such as dimethyl sulfoxide (DMSO-d_6), deuterated chloroform ($CDCl_3$), or other appropriate solvents. Compounds of the present invention can be prepared by synthetic schemes outlined below:

SCHEME I



The following discussion provides the experimental details for the synthetic Scheme I above:

N-(6-Acetylamino-pyridin-3-yl)-N'-(2,2-dimethyl -propionyl) -hydrazinecarboxylic acid *tert*-butyl ester (**II**).

A mixture of N-(5-bromo-pyridin-2-yl)acetamide (**I**) (15.05 g, 70 mM) and THF (150 mL) was mixed with a solution of BuLi in hexanes (2.5 M, 70 mL,175 mM) at -78°C . The resulting solution was agitated for 10 min at -78°C. A mixture of di-tert-butylazodicarboxylate (20.1 g, 87.5 mM) and THF (40mL) then was added, and the reaction mixture was agitated for 25-30 min at about -78°C. The reaction mixture was warmed to ambient temperature and agitated for about 1 h. The mixture was combined with ice, the pH was adjusted to about 7 with 1N HCl, and the cold reaction mixture was washed with ether (x2). The combined ether extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to form a residue. The residue was purified by column chromatography on silica gel

using ethyl acetate / hexanes as the eluent (30:70) to afford 5.9 g (24%) of **II** as an oil.

NMR-^{1}H ($CDCl_3$) δ: 1.47 (s, 18H), 2.20 (s, 3H), 7.55 (br. s, 1H), 7.79 (d, *J*=8.8 Hz, 1H), 8.17 (d, *J*=8.8 Hz, 1H), 8.32 (br s, 1H), 8.64 (s, 1H).

N-(5-Hydrazino-pyridin-2-yl)-acetamide dihydrochloride (**III**)

A mixture of **II** (5.2 g , 14.2 mM) and DCM (15 mL) was mixed with 4N HCl in dioxane (15 mL) and the resulting reaction mixture was let stand for about 18h to form a precipitate. The precipitate was isolated, washed sequentially with (DCM and ether) and dried under reduced pressure (vacuum) to afford 3.8 g (98%) of **III** as a white powder.

MS (MH+): found: 167.0; calc.: 166.09.

(3-{1-[(6-Acetylamino-pyridin-3-yl)-hydrazono]-3-phenyl-propyl}-5-chloro-4-hydroxyphenyl-acetic acid (**V**).

A mixture of **III** (1.3 g, 5 mM), [3-chloro-4-hydroxy-5-(3-phenyl-propionyl)-phenyl]-acetic acid (**IV**) (1.0 g,3.3 mM) and ethanol (15 mL) was diluted with triethylamine to adjust the pH to about 9.5. The resulting mixture was refluxed for 2.5-3h and the solvent was removed under reduced pressure to yield a residue. The residue was treated with 5% aqueous citric acid to form a precipitate. The resulting precipitate was filtered, washed with H_2O and dried in a vacuum oven over P_2O_5, to afford 2.0 g (98%) of **V** as a white solid.

MS (MH+): found: 468; calc. 466.14.

[3-(5-Acetylamino-3-benzyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-acetic acid (**VI**).

A mixture of (**V**) (0.8g,1.88 mM) and a polyphosphoric acid (~6mL) was heated at 125°C for 45-60 min. The reaction mixture was cooled and the resulting suspension was neutralized with 50% NaOH, while maintaining the temperature of the reaction mixture at or below ambient temperature, to

form a precipitate. The precipitate was isolated, washed with water, and purified by reverse phase HPLC (acetonitrile/0.02 N HCl gradient) to give 90 mg (12%) of **VI** as an off-white solid.

NMR-^{1}H (DMSO-d_6) δ: 2.15 (s, 3H), 3.60 (s, 2H), 4.12 (s, 2H), 6.91-7.25 (m, 7H), 7.41 (s, 1H), 7.54 (br. s, 1H), 8.03 (br s, 1H), 9.75 (br. s, 1H).

MS (MH+): found: 450.0; calc.: 449.11.

Ex. 1: [3-(5-Amino-3-benzyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-acetic acid hydrochloride (**VII**, R^2=CH_2COOH)

A mixture of **VI** (88 mg, 0.196mM) and 3N HCl was refluxed for 45-130 min. The solvent was evaporated under reduced pressure to yield a residue. The residue was washed with cold water and dried over P_2O_5 under reduced pressure (vacuum) to yield 86 mg (98%) of **VII** as an off-white solid.

NMR-^{1}H (DMSO-d_6) δ: 3.54 (s, 2H), 4.03 (s, 2H), 6.63 (d, *J*=9.2 Hz, 1H), 6.79-7.27 (m, 6H), 7.35 (s, 1H), 7.51 (br. s, 1H), 7.98 (d, *J*=9.2, 1H), 9.65 (br s, 1H), 12.06 (s, 1H), 12.29 (br s, 1H), 13.81 (br s, 1H).

MS (MH+) : found: 408.1; calc.: 407.10.

Ex. 2: 3-[3-(5-Amino-3-benzyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-propionic acid hydrochloride(**VII**, R^2=CH_2CH_2COOH)

This compound was prepared using the procedure in **X** above.

NMR-^{1}H (DMSO-d_6) δ: 2.39 (t,*J*=7.X , 2H), 2.63 (t, *J*=7.6 Hz, 2H), 4.05 (s, 2H), 6.63 (d, *J*=9.2 Hz, 1H), 6.92 (s, 1H), 7.00-7.18 (m, 5H), 7.31 (s, 1H), 7.46 (br s, 1H), 7.98 (d, *J*=9.2 Hz, 1H), 9.55 (br s, 1H), 12.03 (s, 1H), 13.67 (br s, 1H).

MS(MH+): found: 421.9; calc.: 421.12.

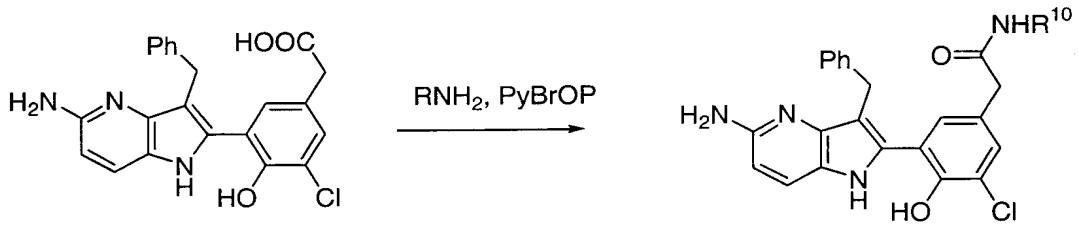
Ex. 3: [5-(5-Amino-3-benzyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-acetic acid hydrochloride (**VII**, R^1= 3-nitrophenyl).

MS (MH+): found: 495.2; calc.: 494.16.

Ex. 21:
NMR-^{1}H (DMSO-d_6) δ: 2.22 (s, 3H), 3.44 (s, 2H), 4.05 (s, 2H), 6.76-7.23 (m, 6H), 7.7.25-7.57 (m, 2H), 7.85 (s, 1H), 9.60 (s, 1H), 11.96 (s, 1H) .
MS: found(MH+) 421.9, calc. 421.12

Ex. 22:
MS: found (M+H) 436.0, calc 437.04

SCHEME II



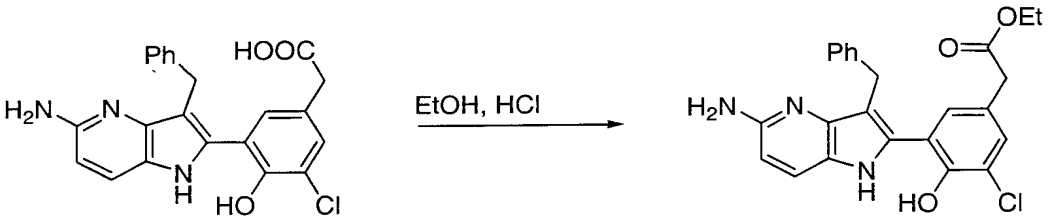
VIII

Ex. 15: 2-[3-(5-Amino-3-benzyl-1*H*-indol-2-yl)-5-chloro-4-hydroxy-phenyl]-acetamide hydrochloride (**VIII**, R^{10} = H)

This compound was prepared by treating the corresponding carboxylic acid with an excess of ammonia solution and PyBrOP, with DMF as the reaction medium, followed by purification on a reverse phase HPLC column using acetonitrile/0.02N HCl gradient.
MS(MH+): found: 407.2; calc.: 406.12.

Ex. 16: 2-[3-(5-Amino-3-benzyl-1*H*-indol-2-yl)-5-chloro-4-hydroxy-phenyl]-*N*-(2-morpholin-4-yl-ethyl)-acetamide dihydrochloride (**VIII**, R = CH_2CH_2-N-morpholinyl).
MS(MH+): found:520.3; calc.: 519.2.

SCHEME III



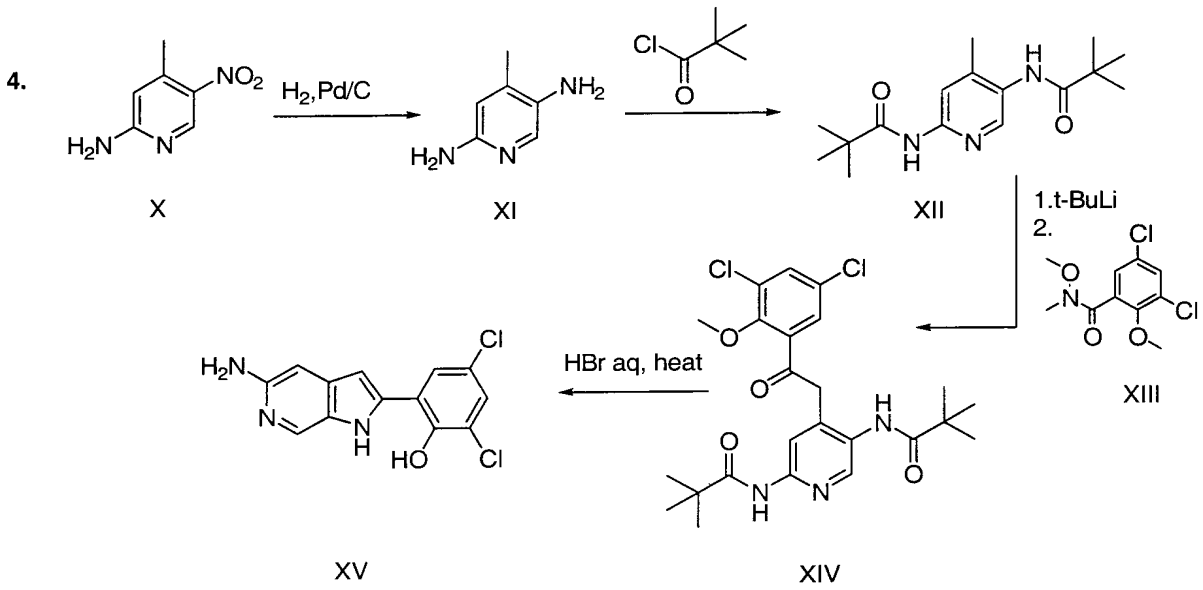
IX

Ex.: 18: [3-(5-Amino-3-benzyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-acetic acid ethyl ester hydrochloride (**IX**)

This compound was prepared by heating the solution of the corresponding carboxylic acid in ethanol with 3N HCl in dioxane. After evaporation of the solvents the residue was redissolved in 5% acetonitrile in water and lyophilized.

MS(MH+) : found: 436.1; calc.: 435.13.

SCHEME IV



X XI XII XIII

XV XIV

2,5-Diamino-4-methylpyridine (**XI**)

A heterogeneous mixture of 2-amino-4-methyl-5-nitropyridin (**X**) (0.83 g, 5,4 mM), 10 % Pd/C (0.24 g) and THF (15 mL) was agitated under 50 psi of hydrogen for 3h. The reaction mixture was filtered through celite, and concentrated under reduced pressure to yield **XI** as an off white crystalline solid.

N-[6-(2,2-Dimethyl-propionylamino)-4-methyl-pyridin-3-yl]-2,2-dimethyl-propionamide (**XII**)

A mixture of XI (0.66 g, 5.4 mM), from above, triethylamine (1.2g, 12 mM) and THF (25 mL) was agitated at 5-10° C. The agitated mixture then was combined with trimehtylacetyl chloride 91.46 g, 11.9 mM) and a catalytic amount of DMAP. The resulting mixture was agitated for 8-16h, diluted with a 5% solution of citric acid, and extracted with ethyl acetate. The combined organic extracts were sequentially washed with water and brine, dried ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure to yield a residue. The residue was purified by column chromatography on silica gel with ethyl acetate / hexanes as the eluent (25:75) to afford 0.95 g (60%) of **XII** as a white powder.
NMR-^{1}H ($CDCl_3$) δ: 1.30 (s, 9H), 1.33 (s, 9H), 2.23 (s, 3H), 7.15 (s, 1H), 7.99 (s, 1H), 8.15 (s, 1H), 8.47 (s, 1H).

3,5-Dichloro-2,*N*-dimethoxy-*N*-methyl-benzamide (**XIII**)

A mixture of 3,5-dichloro-2-methoxy benzoic acid (1.7 g, 7.17 mM), N,O-dimethylhydroxylamine (0.9 g, 9 mM), PyBrOP (4.4 g, 9.3 mM), HOBt (1.25 g, 9.3 mM), triethylamine (2.9 g, 28.8 mM) and DMF (25 mL) was agitated for 4 h at ambient temperature. This reaction mixture then was diluted with water and extracted with a mixture of ethyl ether /ethyl acetate. The combined extracts were sequentially washed with 5% aqueous sodium bicarbonate (2x), H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a residue. The residue was

purified by column chromatography on silica gel with hexane/ethyl acetate 4:1 as the eluent to afford 1.1 g (61%) of **XIII** as a white solid.
MS (MH+): found: 263.8; calc.: 263.0.

N-[4-[2-(3,5-Dichloro-2-methoxy-phenyl)-2-oxo-ethyl]-6-(2,2-dimethyl-propionylamino)-pyridin-3-yl] -2,2-dimethyl-propionamide (**XIV**)

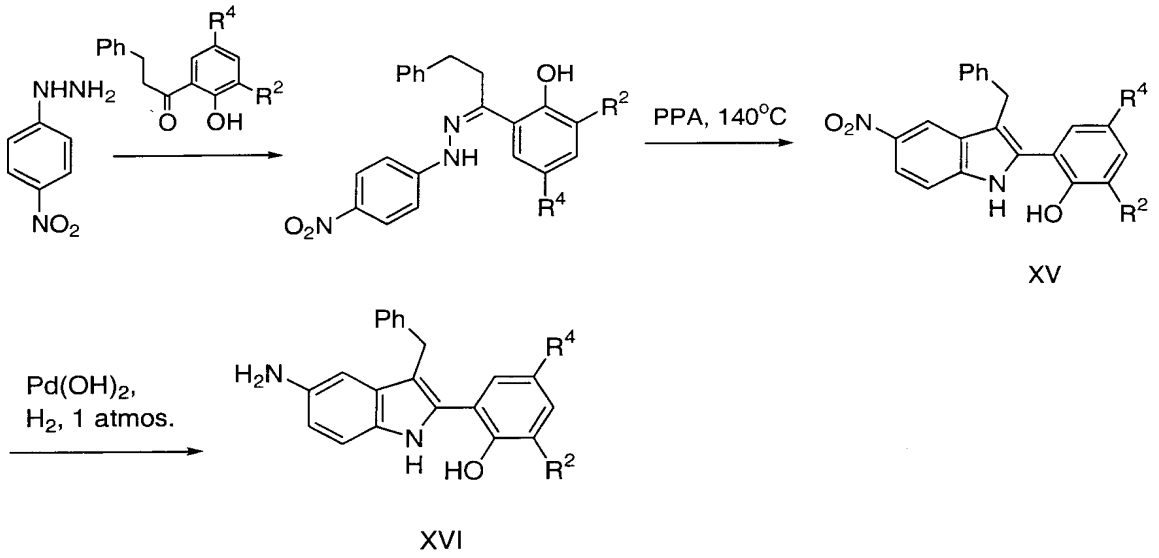
A mixture of **XII** (0.78g, 2.7 mM) and THF (10 mL) was cooled to about -40° C. This cold mixture was combined with t-BuLi in hexanes (1.7M, 6.2 mL, 10.5 mM). The resulting mixture was agitated at about -40° C for 1h. This agitated mixture then was combined with a THF solution of **XIII** (1.06 g, 4.0 mM). This mixture was let stand at about -40°C for 3h, warmed to ambient temperature and let stand at ambient temperature for 15-20h. The reaction mixture then was mixed with an aqueous 5% citric acid mixture and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure to yield a residue. The residue was recrystallized from ethyl acetate-hexane to afford 0.68 g (51%) of **XIV** as a white solid.
MS (MH+): found: 494.1; calc.: 493.15.

Ex. 101: 2-(5-Amino-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-4,6-dichlorophenol hydrochloride (**XV**)

A solution of **XIV** (0.2 g 0.4 mM) in 33% aqueous HBr (10 mL) was refluxed for 6h. After cooling a yellow precipitate was filtered, washed with water, 5% solution of sodium bicarbonate , water and dried in a high vacuum over phosphorus pentoxide to give 0.086 g (72%) of **XV** as a yellow powder. The material was further purified by reverse phase HPLC (acetonitrile/0.02 N HCl gradient) to generate the HCl salt of **XV**.
NMR-^{1}H (DMSO-d_6) δ: 6.62 (br.s, 2H), 6.92 (s, 1H), 7.04 (s, 1H), 7.69 (d, *J*=2.2 Hz, 1H), 7.85 (d, *J*=2.2 Hz, 1H), 8.32 (s, 1H), 10.66 (br.s, 1H), 12.00 (s, 1H), 13.01 (br s, 1H).

MS (MH+): found: 293.9; calc.: 293.01.

SCHEME V



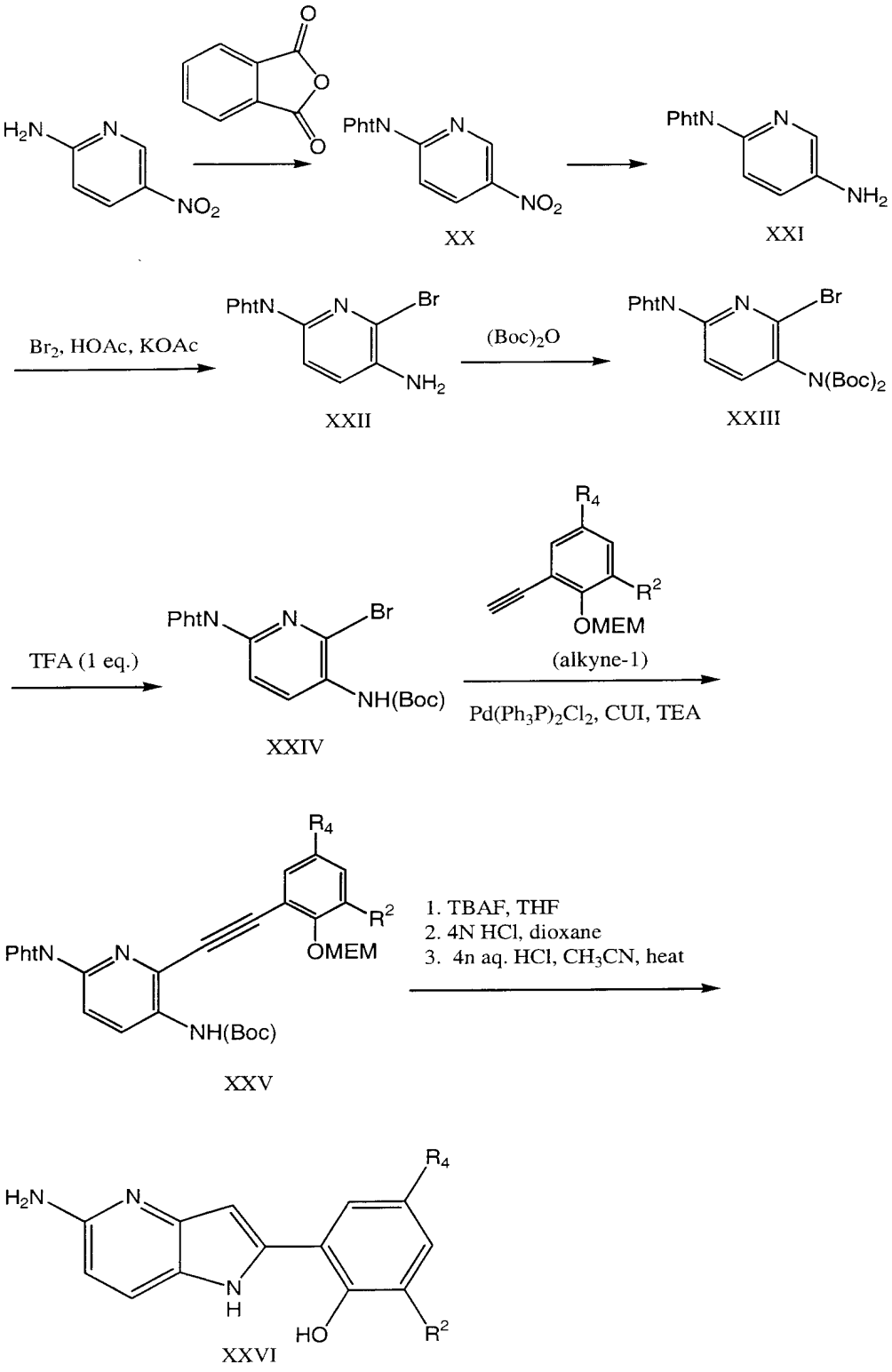
[3-(3-Benzyl-5-nitro-1*H*-indol-2-yl)-5-chloro-4-hydroxy-phenyl]-acetic acid (**XV**)

This compound was prepared by using the procedure to synthesize compound **VI** in Scheme I abovce. The compound was purified by reverse phase HPLC(acetonitrile/0.02N HCl gradient).
MS: found (MH-) 435.0, calc 436.08.

Ex. 201: [3-(5-Amino-3-benzyl-1*H*-indol-2-yl)-5-chloro-4-hydroxy-phenyl]-acetic acid hydrochloride (**XVI**)

This compound was prepared by reducing the corresponding nitro precursor by using the procedure to make compound **XI** in Scheme IV above. Purification by reverse phase HPLC (acetonitrile/0.02N HCl gradient) yielded the title compound.
MS (MH+): found: 407.2; calc.: 406.11.

Scheme VI



2-(5-Nitro-pyridin-2-yl)-isoindole-1,3-dione (XX)

2-amino-5-nitropyridine (30.00g, 215.6mol), phthalic anhydride (35.50g, 239.7mol) and DMF (10 mL) were heated at about 210°C in a sand bath for about 3h. The reaction mixture was cooled to ambient temperature and let stand for about 2h leading to the formation of crystals. The crystals were isolated and washed with ethanol (x2) to yield the compound of formula XX. (53.0g, 91%).
MS: found (MH+) 270.2 , calc 269.21.

2-(5-Amino-pyrdin-2-yl)-isoindole-1,3-dione (**XXI**)

A mixture of con. HCl (500 mL) and XX (20.00g, 74.3mmol) was cooled to about 70°C. A solution of tin(11) chloride dihydrate (50.35g, 223.2mmol) and conc. HCl (60 mL) was mixed with a solution of XX and HCl at about 0°C, and resulting solution was allowed to warm to ambient temperature. The reaction mixture then was mixed with 600 mL water and the resulting reaction mixture was agitated for about 10 minutes to form a bright yellow reaction mixture. This reaction mixture was washed with 4n HCl (x1) and the washed reaction mixture was concentrated under reduced pressure to yield a compound of formula **XXI** (26.87g, >100%).
MS: found (MH+) 240.2 , calc 239.23

2-(5-Amino-6-bromo-pyridin-2-yl)-isoindole-1,3-dione (**XXII**)

A solution of **XXI** (crude 26.87g) in acetic acid (100 mL) was mixed with a solution of KOAc (7.3g, 74.4mmol) in acetic acid (100 mL). The resulting reaction mixture then was mixed with a solution of Br_2 (4.19 mL, 81.8mmol) in acetic acid (50 mL) to form a new reaction mixture. The new reaction mixture then was agitated at ambient temperature for about 12-16 hours. The agitated reaction mixture then was diluted with water (600 mL) and the resulting mixture was agitated for about 10 minutes. The reaction solids were isolated, dried and dissolved in methylene chloride. The methylene chloride solution was filtered through celite and the filtered methylene chloride solution was concentrated under reduced pressure to yield the compound of formula **XXII** (18.14g, 76%).
MS: found (MH+) 319.0 , calc 318.13.

[2-Bromo-6-(1,3-dihydro-isoindol-2-yl)-pyridin-3-yl]-biscarbamic acid tert-butyl ester (**XXIII**)

A solution of **XXII** (9.90g, 31.1mmol) in THF (250 mL) was mixed with Et_3N (19.4 mL, 139mmol), di-*tert*-butyl dicarbonate ($(Boc)_2O$) (21.72g, 99.4mmol), and DMAP (catalytic) to form a reaction mixture. The reaction mixture was agitated at ambinet temperature from about 8 to about 16 hours. The agitated reaction mixture then was mixed with 5% citric acid until the pH of the reaction mixture reached about 5. The pH adjusted reaction mixture then was extracted with ethyl acetate and the ethyl acetate layer was sequentially washed with water (x1) and brine (x1), dried (Na_2SO_4) and concentrated under reduced pressure to yield the compound of formula **XXIII** (13.4g, 83%).

MS: found (MH+) 519.4 , calc 518.36

[2-Bromo-6-(1,3-dihydro-isoindol-2-yl)-pyridin-3-yl]-carbamic acid tert-butyl ester (**XXIV**)

A solution of **XXIII** (4.73g, 9.12mmol) and CH_2Cl_2 (25mL) was mixed with CF_3COOH (1.25mL, 16.2mmol) at about 0°C. The reaction mixture then was warmed to ambient temperature and agitated at ambient temperature for about 6h. The agitated reaction mixture then was concentrated under reduced pressure to yield a residue. The residue was diluted with ethyl acetate and the pH of the reaction mixture was adjusted to about 5 using a 5% aqueous solution of citric acid. The organic layer was isolated, and sequentially washed with water (x1) and brine (x1), dried ($MgSO_4$) and then concentrated under reduced pressure to yield a residue. The residue was diluted with ethyl acetate and the ethyl acetete solution was cooled in a freezer for about 12 hours leading to the formation of crystals. The crystals were isolated, washed with ethyl acetate, and dried under reduced pressure to yield the compound of formula **XXIV** (2.80g, 73%).

^{1}H-NMR (DMSO-d_6) δ: 8.13 (d, 1H), 7.92 (m, 2H), 7.57 (s, 1H), 1.48 (s, 9H).

MS: found (MH+) 419.4 , calc 418.24.

Compound **XXV**

A mixture of alkyne-1 (0.47 g,1.00 mmol) and dry acetonitrile was combined with the compound of formula **XXIV** 0.42 g (1.00 mmol) to form a mixture. The mixture then was mixed with Et_3N (10.0 mmol, 1.4 mL) and nitrogen gas was bubbled through the reaction mixture for a couple of minutes. The preceeding reaction mixture then was mixed with CuI (3.8 mg, 0.02 mmol) and dichlorobis(triphenylphosphine)-palladium(II) (14.0 mg, 0.02 mmol) to form a new reaction mixture. The new reaction mixture then was refluxed for about an hour. The refluxed reaction mixture was cooled to ambinet temperature and the cooled reaction mixture was quenched with with 5% citric acid/EtOAc leading to the formation of a solid. The solid was isolated and purified by column chromatography on 10 g of silica (EtOAc/hexane) to yield the compound of formula **XXV** (0.37 g (45%).

^1H NMR ($CDCl_3$) δ: 1.51 (s, 9H), 2.66 76 (d d, J = 6 Hz, 18 Hz, 1H), 3.10-3.20 (m, 6H), 3.25-3.35 (m, 2H), 3.62 (s, 3H), 3.65 (s, 3H), 4.06 (d d, J = 6 Hz, 11 Hz, 1H), 5.00 (s, 2H), 7.27 (d, J = 3 Hz, 1H), 7.31 (d, J = 9 Hz, 1H), 7.52 (d, J = 3 Hz, 1H), 7.55 (t, J = 7 Hz, 1H), 7.70-7.80 (m, 2H), 7.81 (d d, J = 1 Hz, 7 Hz,), 7.87-7.93 (m, 2H), 8.17 (d of m, J = 7 Hz, 1H), 8.39 (d, J = 1 Hz, 1H), 8.70 (d, J = 9 Hz, 1H).

Compound **XXVI** (**Ex. 401**) (R^2 = *m*-nitrophenyl, R^4=4-(1,2-dicarboxy-ethyl)

A solution of the compound of formula **XXIV** (0.3 g, 0.38 mmol) and 3.0 mL of 1.0 M TBAF in THF was agitated at elevated temperatures (about 65°C) for about 4h. The raction mixture then was cooled to ambinet temperature, mixed with 5% citric acid/EtOAc and extracted with EtOAc. The EtOAc extracts were dreid ($MgSO_4$) and then concentrated under reduced pressure to yield crude pyrrolo[b]pyridine as a residue. The crude product then was dissolved in 2 ml dry methanol and 2 mL 4M

HCl/dioxane. The resulting mixture was agitated for about 6 hours. The agitated reaction mixture was mixed with a sodium bicarbonate solution/EtOAc, the organic layer was isolated and washed with water. The aqueous layer was further acidified to a pH of about 2, and extracted with EtOAc. The organic layers were combined, dried 9sodium sulfate) and concentrated under reduced pressure to yield a residue. The crude residue was further dissolved in acetonitrile (4 mL) and 4N HCl(4 mL) and the resulting mixture was heated to reflux for about 12 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure to yield a residue. The residue was purified using preparative HPLC to yield the compound of formula **XXVI** (64 mg, 34%).

^{1}H NMR (DMSO-d_6) δ: 2.52 (d d, J = 6. 2 Hz, 1H), 3.01 (m, 1H), 3.84 (m, 1H), 6.49 (d, J = 9 Hz, 1H), 6.78 (s, 1H), 7.16 (d, J = 2 Hz, 1H), 7.39 (br s, 1H), 7.57 (d, J = 2 Hz), 7.65 (t, J = 7 Hz, 1H), 7.86 (d, J = 7 Hz, 1H), 7.91 (d, J = 9 Hz, 1H), 8.11 (d, J = 7 Hz, 1H), 8.24 (s, 1H).

MS: found (MH+) 463.3, calc 462.41.

The following examples were prepared using the procedure outlined in Scheme VI above.

Ex. 402:

^{1}H NMR (DMSO-d_6) δ: 2.61 (m, 4H), 3.42 (virt. Quint, J=8.4 Hz, 1H), 6.56 (d, J=10.2 Hz, 1H), 6.86 (s, 1H), 7.24 (s, 1H), 7.46 (br. s , 2H), 7.63 (s, 1H), 7.69-7.75 (m, 1H), 7.91 (d, J=8.1 Hz, 1H), 8.00 (d, J-10.2 Hz, 1H), 8.18 (d, J=8.1 Hz, 1H), 8.33 (s,1H), 12.06 (br s, 1H).

MS found (MH+) 477.4, calc. 476.13.

Ex. 403:

^{1}H NMR (DMSO-d_6): 3.65 (s, 2H), 6.61 (d, J= 8.8 Hz, 1H), 6.88 (s, 1H), 7.16 (s,1H), 7.61-7.37 (m, 6H), 8.05 (d, J=8.8 Hz, 1H), 9.06 (br s, 1H), 12.05 (br.s, 1H),

13.79 (br. s, 1H). MS; found (MH=) 360.0, calc. 359.13.

Ex. 404:

^{1}H NMR (dmso-d_6) δ : 3.63 (s, 2H), 6.60 (d, J=9.1 Hz, 1H), 6.87 (s, 1H), 7.27 (s, 1H), 7.57 (br s, 1H), 7.67 (s, 1H), 7.76 (t, J=8.1 Hz, 1H), 7.96 (d, J=8.1 Hz, 1H), 8.04 (d, J=9.1 Hz, 1H), 8.23 (d, J=8.4 Hz, 1H), 8.36 (s, 1H), 9.62 (s, 1H), 12.43 (br.s, 2H), 14.07 (br. s, 1H).
MS: found (MH+) 405.1, calc 404.1.

Ex. 405:

^{1}H NMR(DMSO-d_6) δ: 6.66(d, J=7.7 Hz, 1H), 7.03 (s, 1H), 7.65 (s, 1H), 7.85 (br t, 1H), 8.11-8.05 (m, 3H), 8.30 (d, J=7.7 Hz, 1H), 8.47 (s, 1H). 8.54 (s, 1H), 12.35 (br.s, 1H), 13.95 (br.s, 1H).
MS: found (MH+) 414.3, (M-H) 413.0, calc 414.12.

Ex. 406:

^{1}H NMR (DMSO-d_6): 2.56 (br t, 2H), 2.82 (br t, 2H), 6.62 (d, J=8.1Hz, 1H), 6.91 (s, 1H), 7.27 (s, 1H), 7.57 (br s, 1H), 7.65 (t, J=7.7 Hz, 1H), 8.05 (d, J=8.1 Hz, 1H), 8.16 (d, J=9.1 Hz, 1H), 8.25 (d, J=7.7 Hz, 1H), 8.39 (s, 1H), 9.36 (s, 1H), 12.18 (br. s , 1H), 13.76 (br s, 1H).
MS: found (MH+) 419.3, calc 418.13.

Ex. 407:

^{1}H NMR (DMSO-d_6): 3.57 (s, 2H), 6.63 (d, J=9.1 Hz, 1H), 6.91 (s, 1H), 7.34 (s, 1H), 7.62 (br s, 3H), 8.03(d, J=9.1 Hz, 1H).
MS: found (M-H) 315.8, calc 317.06.

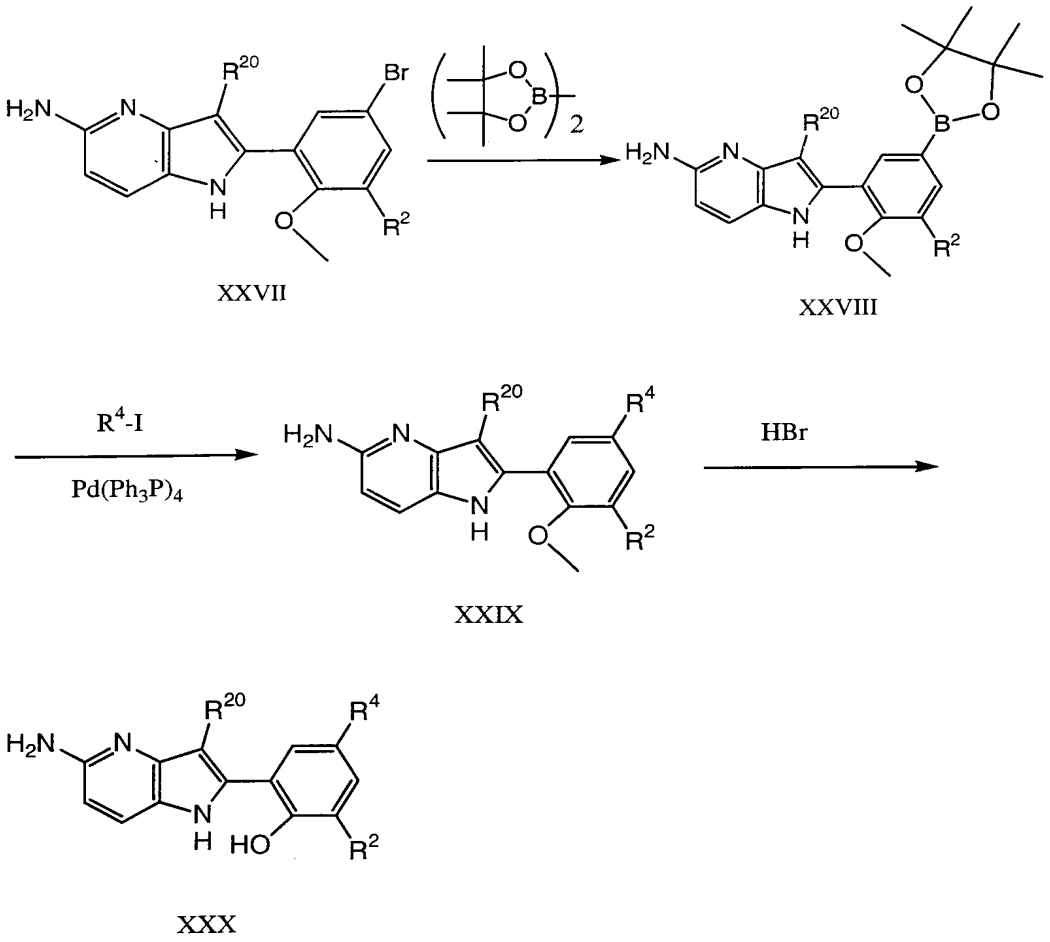
Ex. 408:

^{1}H NMR (DMSO-d_6): 2.68 (br.t, 2H), 2,92 (br t, 2H), 6.63 (d, J=8.8 Hz, 1H), 6.94 (s, 1H), 7.31 (s, 1H), 7.62 (br s, 3H), 8.04 (d, J-8.8 Hz, 1H), 10.00 (br s, 1H), 12.20 (br s, 1H), 13.97 (br s, 1H).
MS: found (MH+) 331.9, calc 331.07.

Ex. 409:

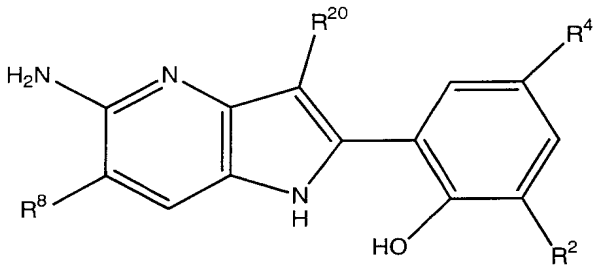
MS: found (MH+) 366.4, calc 365.08

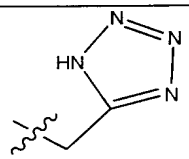
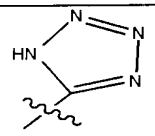
Scheme VII



Tables I-VII list compounds that can be made using the synthetic schemes and procedures discussed above.

Table I:



Ex.	R^2	R^4	R^8	R^{20}
1	Cl	CH_2COOH	H	benzyl
2	Cl	CH_2CH_2COOH	H	benzyl
3	Cl	CH_2CONHR^{10}	H	benzyl
4	Ph	CH_2COOH	H	benzyl
5	Ph	CH_2CH_2COOH	H	benzyl
6	Br	CH_2CH_2COOH	H	benzyl
7	Br	CH_2COOH	H	benzyl
8	Cl	COOH	H	benzyl
9	Br	COOH	H	benzyl
10	3-nitro-phen-1-yl	CH_2COOH	H	benzyl
11	3-nitro-phen-1-yl	CH_2CH_2COOH	H	benzyl
12	Br		H	benzyl
13	3-nitro-phen-1-yl	COOH	H	benzyl
14	Br		H	benzyl

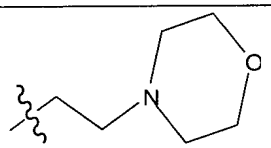
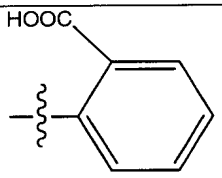
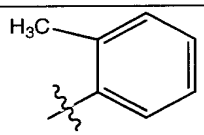
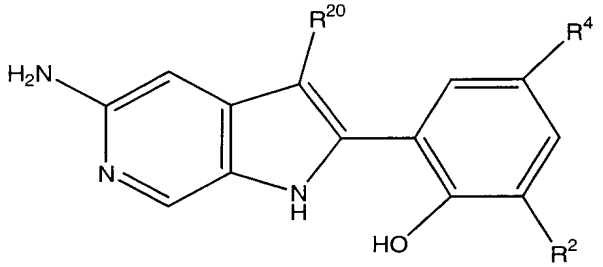
Ex.	R^2	R^4	R^8	R^8
15	Cl	CH_2CONH_2	H	benzyl
16	Cl		H	benzyl
17	Cl	$C(CH_3)COOH$	H	benzyl
18	Cl	$CH_2COOC_2H_5$	H	benzyl
19	Cl	CH=CH-COOH	H	benzyl
20	Cl		H	benzyl
21	Br	CH_2COOH	CH_3	benzyl
22	Br	COOH	H	benzyl
23	Cl	Br	H	benzyl
24	Cl	COOH	H	benzyl
25	Cl		H	benzyl

Table II:



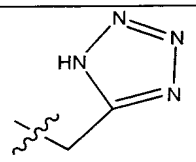
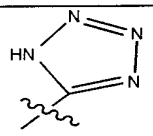
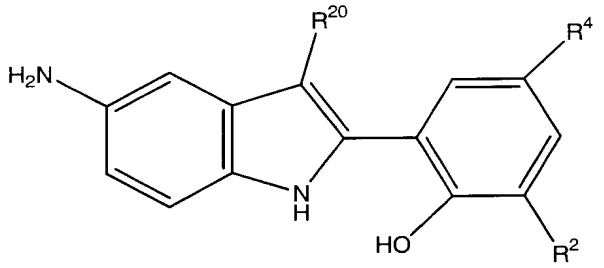
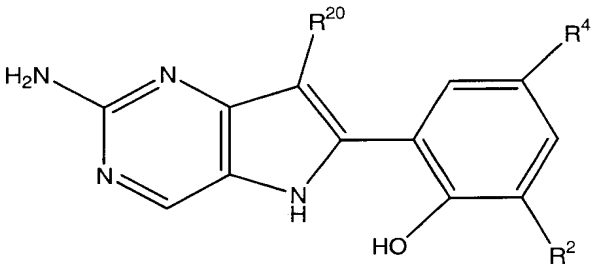
Ex.	R^2	R^4	R^{20}
101	Cl	Cl	H
102	Cl	CH_2COOH	CH_2Ph
103	Ph	CH_2COOH	CH_2Ph
104	Br	CH_2COOH	CH_2Ph
105	Ph	CH_2CH_2COOH	CH_2Ph
106	Ph	CH_2CH_2COOH	CH_2Ph
107	Br	CH_2COOH	CH_2Ph
108	Cl	COOH	CH_2Ph
109	Br	COOH	CH_2Ph
110	3-nitro-phen-1-yl	CH_2COOH	CH_2Ph
111	3-nitro-phen-1-yl	CH_2CH_2COOH	CH_2Ph
112	Br		CH_2Ph
113	3-nitro-phen-1-yl	COOH	CH_2Ph
114	Br		CH_2Ph
115	Cl	CH_2CONH_2	CH_2Ph

Table III:



Ex.	R^2	R^4	R^{20}
201	Cl	CH_2COOH	CH_2Ph
202	Cl	Cl	CH_2Ph
203	Ph	CH_2COOH	CH_2Ph
204	Br	CH_2COOH	CH_2Ph
205	Ph	CH_2CH_2COOH	CH_2Ph
206	Ph	CH_2CH_2COOH	CH_2Ph

Table IV:



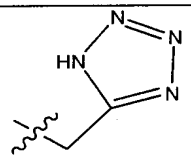
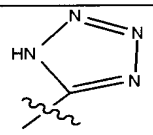
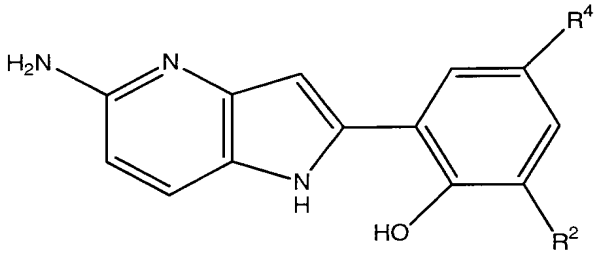
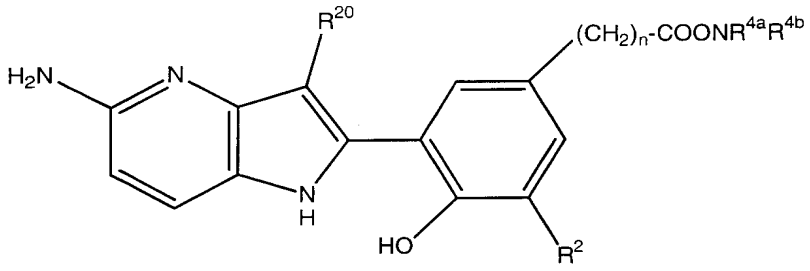
Ex.	R^2	R^4	R^{20}
301	Cl	Cl	H
302	Cl	CH_2COOH	CH_2Ph
303	Ph	CH_2COOH	CH_2Ph
304	Br	CH_2COOH	CH_2Ph
305	Ph	CH_2CH_2COOH	CH_2Ph
306	Ph	CH_2CH_2COOH	CH_2Ph
307	Br	CH_2COOH	CH_2Ph
308	Cl	COOH	CH_2Ph
309	Br	COOH	CH_2Ph
310	3-nitro-phen-1-yl	CH_2COOH	CH_2Ph
311	3-nitro-phen-1-yl	CH_2CH_2COOH	CH_2Ph
312	Br		CH_2Ph
313	3-nitro-phen-1-yl	COOH	CH_2Ph
314	Br		CH_2Ph
315	Cl	CH_2CONH_2	CH_2Ph

Table V



Ex.	R^2	R^4
401	*m*-nitrophenyl	4-(1,2-dicarboxy-ethyl)
402	*m*-nitrophenyl	4-(2-carboxy-1-carboxymethyl-ethyl)
403	phenyl	CH_2COOH
404	*m*-nitrophenyl	CH_2COOH
405	*m*-nitrophenyl	2-tertazolyl
406	*m*-nitrophenyl	CH_2CH_2COOH
407	Cl	CH_2COOH
408	Cl	CH_2CH_2COOH
409	3-thienyl	CH_2COOH

Table VI



Ex.	n	R^2	R^{4a}	R^{4b}	R^{20}
501	1	*m*-nitro phenyl	H	2-morpholin-4-yl-ethyl	H
502	1	Cl	2-hydroxy ethyl	2-hydroxy ethyl	benzyl
503	1	Cl	CH_2CH_2-SO_2-R^{4b}	CH_2CH_2	benzyl
504	1	Cl	H	2-methoxy ethyl	benzyl
505	1	*m*-nitro phenyl	H	2-hydroxy ethyl	H
506	1	*m*-nitro phenyl	H	2-methoxy ethyl	H
507	1	*m*-nitro phenyl	H	2-(1*H*-imidazol-4-yl)-ethyl	H
508	1	Cl	CH_2CH_2-O-R^{4b}	CH_2CH_2	benzyl
509	1	Cl	$CH(CH_3)CH_2$-O-R^{4b}	$CH(CH_3)CH_2$	benzyl
510	1	*m*-nitro phenyl	H	2-dimethylamino ethyl	H
511	2	Cl	CH_2CH_2-O-R^{4b}	CH_2CH_2	benzyl
512	2	Cl	H	2-morpholin-4-yl-ethyl	benzyl

The compounds in Table VI were prepared suing the procedure outlined in Scheme I above.

Ex. 501:
MS: found (MH+) 517.1, calc 516.21.

Ex. 502:
MS :found (M-H) 493.0 , calc 494.17 .

Ex. 503:
MS: found (MH+) 525.2 ,calc 524.13.

Ex. 504:
MS: found (MH+) 464.9 , calc 464.16 .

Ex. 505
MS:found (MH+) 492.2, calc 491.18.

Ex. 506:
MS:found (MH+) 461.6, calc 461.17.

Ex. 507:
MS:found (MH+) 498.5, calc 497.18.

Ex. 508:
MS:found (MH+) 477.1, calc 476.16.

Ex. 509:
MS:found (MH+) 504.8, calc 504.19.

Ex. 510:
MS:found (MH+) 475.1, calc 474.20

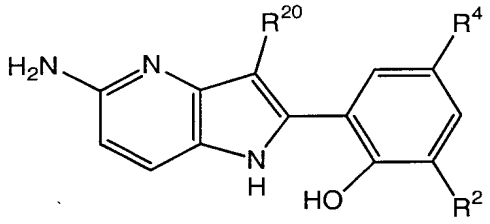
Ex. 511
^{1}H NMR (CD_3OD) δ: 2.43 (t, J = 8 Hz, 2H,), 2.66 (t, J = 8Hz, 2H) , 3.25 (m, 2H), 3.38 (m, 6H), 4.05 (s, 2H), 6.57 (d, J = 10

Hz, 1H), 6.91 (d, J = 2.5 Hz, 1H), 6.95-7.18 (m, 5H), 7.21 (d, J = 2.5 Hz, 1H), 7.92 (d, J = 10 Hz, 1H).
MS: found (MH+) 491.0, calc 490.18.

Ex. 512

^{1}H NMR (CD_3OD) δ: 2.44 (t, J = 7 Hz, 2H), 2.76 (t, J = 7 Hz, 2H), 3.0-3.24 (m, 4H), 3.48 (m, 4H), 3.75 (t, J = 11 Hz, 2H), 3.99 (m, 2H), 4.13 (s, 2H), 6.66 (d, J = 10 Hz, 1H), 7.00 (d, J = 2 Hz, 1H), 7.02-7.26 (m, 5), 7.27 (d, J = 2 Hz, 1H), 8.01 (d, J = 10 Hz, 1H).
MS: found (MH+) 534.0, calc 533.22.

Table VII



Ex.	R^2	R^4	R^{20}
601	Cl	Ph	benzyl
602	Cl	Ph	H
603	Cl	*o*-cyano phenyl	H
604	Cl	*o*-carboxy phenyl	benzyl
605	Cl	*o*-carboxyphenyl	benzyl
606	Cl	*p*-methoxycarbonyl phenyl	benzyl
607	Cl	*o,m*-bis(methoxy carbonyl)phenyl	benzyl

Compounds listed in Table VII were preapred by using the procedure outlined in Scheme VII.

Ex. 601:

5-(5-Amino-3-benzyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)-3-chloro-biphenyl-4-ol

^{1}H-NMR (d_6-DMSO) δ ppm: 14.20 (bs, 1H), 12.27 (bs, 1H), 10.00 (bs, 1H), 8.06 (d, J = 8.9 Hz, 1H), 7.78 (d, J = 2.3 Hz, 1H), 7.66 (bs, 2H), 7.43-7.07 (m, 11H), 6.71 (d, J = 9.1 Hz, 1H), 4.18 (s, 2H);

^{13}C NMR (d_6-DMSO) δ ppm: 151.68, 150.07, 140.39, 137.80, 136.47, 132.33, 130.30, 129.39, 128.85, 128.34, 128.17, 127.83, 127.75, 127.34, 126.07, 125.86, 122.49, 122.39, 121.43, 106.56, 104.69, 28.49.

MS LCMS MH+ 426.14 (calc.), 426.6 (obs.).

Ex. 602:

5-(5-Amino-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)-3-chloro-biphenyl-4-ol

^{1}H-NMR (d_6-DMSO) δ ppm: 14.08 (bs, 1H), 12.47 (bs, 1H), 10.27 (bs, 1H), 8.07 (m, 2H), 7.80-7.70 (m, 4H), 7.47 (t, 3H), 7.38 (d, J = 7.4 Hz, 1H), 7.10 (s, 1H), 6.69 (d, J = 8.9 Hz, 1H);

^{13}C NMR (d_6-DMSO) δ ppm: 151.34, 149.46, 138.19, 137.77, 133.16, 131.20, 129.26, 128.90, 127.54, 127.48, 126.52, 124.79, 123.08, 123.04, 120.94, 105.08, 96.39:

MS LCMS (MH+) 336.09 (calc.), 336.2 (obs.).

Ex. 603:

5'-(5-Amino-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)-3'-chloro-4'-hydroxy-biphenyl-2-carbonitrile

MS LCMS MH+ 361.09 (calc.), 360.9 (obs.).

Ex. 604:

5'-(5-Amino-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)-3'-chloro-4'-hydroxy-biphenyl-2-carboxylic acid (33).

MS LCMS MH+ 380.08 (calc.), 380.2 (obs.).

Ex. 605:

5'-(5-Amino-3-benzyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)-3'-chloro-4'-hydroxy-biphenyl-2-carboxylic acid

MS LCMS MH+ 470.13 (calc.), 470.2 (obs.).

Ex. 606:

5'-(5-Amino-3-benzyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)-3'-chloro-4'-hydroxy-biphenyl-4-carboxylic acid methyl ester

MS: found (MH+) 484.4, calc. 484.13.

Ex. 607:

5'-(5-Amino-3-benzyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)-3'-chloro-4'-hydroxy-biphenyl-2,5-dicarboxylic acid

MS: found (MH+) 514.4, calc. 514.11.

UTILITY

The compounds of this invention are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals. The term "thromboembolic disorders" as used herein includes arterial or venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example unstable angina, first or recurrent ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, kidney embolisms, and pulmonary embolisms. The anticoagulant effect of compounds of the present invention is believed to be due to the inhibition of Factor Xa (FXa), Factor VIIa (FVIIa), and thrombin.

Factor Xa determinations were made in 50 mM Tris buffer, pH 7.5, containing 150 µM NaCl, 5 mM CaCl2, 0.05% Tween-20, and 1.0 mM EDTA. Values of Ki app. were determined by allowing 2-4 nM human Factor Xa (Haematologic Technologies, VT, USA) to react with the 1 mM substrate (MeOC-Nle-Gly-Arg-pNA) in the presence of an inhibitor. Hydrolysis of the chromogenic substrate is followed spectrophotometrically at 405 nm for five minutes. The enzyme assay routinely yielded linear progression curves under these conditions. Initial velocity measurements calculated from the progress curves by a kinetic analysis program (Batch Ki; Peter Kuzmic, BioKin, Ltd., Madison, WI) were used to determine Ki app. Compounds of the present invention are also useful as inhibitors of proteases, which play a significant role in the progression of cancer. Their inhibitory activity includes inhibition of urokinase (uPA) which has been postulated to have therapeutic value in treating cancer.

Some of the compounds of the present invention show selectivity between uPA and FXa, with respect to their inhibitory properties. The effectiveness of compounds of the present invention as inhibitors of Urokinase and Factor Xa is determined using synthetic substrates and purified Urokinase and purified human Factor Xa respectively.

The rates of hydrolysis by the chromogenic substrates were measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrates result in the release of the -pNA moiety, which is monitored spectrophotometrically by measuring the increase in absorbance at 405 nano meter (nm). A decrease in the rate of absorbance change at 405 nm in the presence of a inhibitor is indicative of enzyme inhibition. The results of this assay are expressed as the inhibitory constant, Ki app.

Definitions

The compounds of the present invention may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of materials. Many geometric isomers of olefins, C=N double bonds, and the like can be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure (representing a compound of Formula I) are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

As used herein, the following terms and abbreviations have the following meaning, unless indicated otherwise.

The term "prodrug" is intended to represent covalently bonded carriers which are capable of releasing the active ingredient of Formula I, when the prodrug is administered to a mammalian subject. Release of the active ingredient occurs *in vivo*. Prodrugs can be prepared by techniques known to one skilled in the art. These techniques generally modify appropriate functional groups in a given compound. These modified functional groups however regenerate original

functional groups by routine manipulation or *in vivo*. Prodrugs of compounds of Formula I include compounds wherein a hydroxy, amidino, guanidino, amino, carboxylic or a similar group is modified.

"Pharmaceutically acceptable salts" is as understood by one skilled in the art. Thus a pharmaceutically acceptable salt includes acid or base salts of compounds of Formula I. Illustrative examples of pharmaceutically acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "optionally is substituted with one to three substituents" means that the group referred to may or may not be substituted in order to fall within the scope of the invention. Thus the term "optionally substituted" is intended to mean that any one or more hydrogens on a designated atom can be replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound. When the substituent is keto (=O) then 2 hydrogens on the atom are replaced. "Optional substituents" , unless otherwise indicated, are independently selected from a group consisting of H; $N(R^{10})_2$; NO_2; halogen; aryl; $O-C_{5-10}$ cyclo alkyl substituted with R^{10}; guanidino; urea; thio urea; amidino; para or meta phenoxy; piperidin-4-yloxy; 4-amino-cyclohexyloxy; 1-(1-Imino-ethyl)-piperidin-4-yloxy; 1-(1-Imino-ethyl)-pyrrolidin-3-yloxy; 2-Amino-3-methyl-butyryl;

4-Acetimidoylamino-cyclohexyloxy; $CO-C_{1-4}$ alkyl, 1-(1-Imino-ethyl)-pyrrolidin-2-ylmethoxy; 2-(2-Hydroxycarbonimidoyl-pyridin-3-yloxy)-ethoxy; 3,4-Dicyano-phenoxy; SC_{1-4} alkyl, S-aryl, pyrimidin-2-ol-5-yl, $O-C_{1-4}$ alkyl, $COOR^{10}$, C(O)-pyrrolidine; $C(O)CH(NH_2)CH_2OH$; $C(O)CH(NH_2)CH_2Ph$; $C(O)CH(NH_2)CH_2COOH$; O-pyrrolidine; SO_2-C_{1-4} alkyl, $C(O)-(CH_2)_{1-3}$-imidazole; $SO_2-N(alkyl)_2$; $C(=N)-C_3$; O-piperidine; 2-aminothiazol-5-ylmethoxy; $O-CH_2-COOH$; pyrrolidine-2-ylmethoxy; 2,4,6-triamino pyrimidin-5-ylmethoxy; $NH-SO_2$-alkyl; NHC_1-C_4 alkyl; $N(C_1-C_4)_2$ alkyl; CF_3; C_{2-10} alkenyl and C_{1-10} alkyl.

The term "alkyl", as used herein, is intended to include branched and straight chain saturated aliphatic hydrocarbon groups having from 1 to 14 or the specified number of carbon atoms, illustrative examples of which include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, and n-hexyl. "Alkenyl" is intended to include a branched or straight chain hydrocarbon group having one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like. The term "alkelene" represents an alkyl group, as defined above, except that it has at least one center of unsaturation, i.e., a double bond. Illustrative examples are butene, propene, and pentene. The term "cycloalkyl", "cycloalkyl ring", "cycloalkyl radical" or "cyclic hydrocarbon" indicates a saturated or partially unsaturated three to fourteen carbon monocyclic or bicyclic hydrocarbon moiety which is optionally substituted with an alkyl group. Illustrative examples include cyclo propyl, cyclo hexyl, cyclo pentyl, and cyclo butyl. The term "alkoxy" as used herein represents $-OC_{1-6}$ alkyl.

The terms "Ar" and "aryl", as used herein, are intended to represent a stable substituted or unsubstituted (collectively also referred to as 'optionally substituted') six to fourteen membered mono-, bi- or tri-cyclic hydrocarbon radical comprising carbon and hydrogen atoms. Illustrative examples are phenyl (Ph), naphthyl, anthracyl groups, and

piperanyl. It is also intended that the terms "carbocycle" and "carbocyclic" include "Ar", "aryl" as well as "cyclo alkyl" groups, which are defined above. "Halogen" or "halo", as used herein, represents Cl, Br, F or I.

As used herein the term "bicyclic heterocyclic ring structure" is intended to represent a stable 7 to 10 membered bicyclic heterocyclic ring which is partially unsaturated or unsaturated (aromatic, i.e., heteroaryl) and which consists of carbon atoms and from 1 to 3 hetero atoms selected from S, O, and N, preferably nitrogen atoms. The nitrogen and sulfur atoms can exist in their respective oxidized states, while the nitrogen atom can also exist in its quaternized form. Illustrative examples of the bicyclic heterocyclic ring structure are 3H-imidazo[4,5-c]pyridine-2-yl, 1H-imidazo[4,5-c]pyridine-2-yl, 3H-pyrrolo[3,2-c]pyridine-2-yl, 3H-pyrrolo[3,2-c]pyrimidine-2-yl, thiazolo[5,4-c]pyridine-2-yl, oxazolo[5,4-c]pyridine-2-yl, 4H-thiopyrano[4,3-d]oxazole, 1H-indole-2-yl, 1H-benzimidazole-2-yl, 2,3-dihydro,1H-indole-2-yl, 2,5-dihydro-thiopyrano[2,3-b]pyrrole, thieno[2,3-c]pyridine, 4,5-dihydro-1H-benzoimidazole-2-yl, 1H-pyrrolo[2,3c]pyridine, benzooxazole, 4H-thiopyrano[4,3-b]furan, 4,5-dihydrofuro[3,2-b]pyridine, 1,7-dihydro-thiopyrano-[2,3-b]pyrrole-2-yl, 1,4-dihydro-thiopyrano-[3,4-d]imidazole-2-yl, and 1,5-dihydro pyrano[2,3-d]imidazole-2-yl. It is preferred that when the total number of hetero atoms in the heterocycle exceeds 1, then the heteroatoms are not adjacent to one another. Preferred bicyclic heterocyclic ring structures comprise 9 to 10 membered bicyclic heterocyclic ring structures comprising a six membered ring and a five membered ring fused together such that the two rings have two common atoms. Illustrative examples of the preferred bicyclic heterocyclic ring structures are 1H-indole-2-yl, 1H-benzimidazole-2-yl.

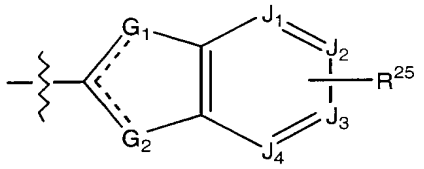
The term "heteroaryl" is intended to represent a stable 5 to 10 membered aryl group ("aryl" as defined above), wherein one or more of the carbon atoms is replaced by a hetero atom selected from N, O, and S. The hetero atoms can exist in their chemically allowed oxidation states. Thus a

Sulfur (S) atom can exist as a sulfide, sulfoxide, or sulfone. Preferred heteroaryl groups are six membered ring systems comprising not more than 2 hetero atoms. Illustrative examples of preferred heteroaryl groups are thienyl, N-substituted succinimide, 3-(alkyl amino)-5,5-dialkyl-2-cyclohexen-1-one, methyl pyridyl, alkyl theophylline, tetrazolyl, furyl, pyrrolyl, indolyl, pyrimidinyl, isoxazolyl, purinyl, imidazolyl, pyridyl, pyrazolyl, quinolyl, and pyrazinyl. The term "heterocycloalkyl" means a stable cyclo alkyl group containing from 5 to 14 carbon atoms wherein one or more of the carbon atoms is replaced by a hetero atom chosen from N, O and S. The hetero atoms can exist in their chemically allowed oxidation states. Thus Sulfur (S) can exist as a sulfide, sulfoxide, or sulfone. The heterocycloalkyl group can be completely saturated or partially unsaturated. Illustrative examples are piperidine, 1,4-dioxane, and morpholine.

As used herein the terms "heterocyclyl", "heterocyclic" and/or "het" are intended to represent a stable 5- to 7-membered monocyclic or 7- to 10- membered bicyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated (aromatic), which consists of carbon atoms and from one to 4 hetero atoms independently selected from a group consisting of N, O and S. The nitrogen and the sulfur hetero atoms can exist in their respective oxidized states. The heterocyclic ring may be attached to its pendent group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on a carbon or a nitrogen atom if the resulting compound is stable. The nitrogen in the heterocycle can exist in its quaternized form. It is preferred that when the total number of hetero atoms in the heterocycle exceeds 1, then the heteroatoms are not adjacent to one another. It is understood that the terms "heterocyclyl", "heterocyclic", and "het" include the terms "heteroaryl", "heterocycloalkyl" and "bicyclic heterocyclic ring structure" as described above.

Preferred "heterocyclyl", "heterocyclic" and/or "het" groups are selected from 1-(2,Hydroxymethyl-pyrrolidin-1-yl)-2,3-dimethyl-butan-1-one, 3-Pyridin-2-yl-propan-1-ol, N-(2,3-Dimethoxy-benzyl)-2-hydroxy-acetamide, 1-Methyl-2-m-tolyl-1H-benzoimidazole-5-carboxamidine, 2-Methyl-3,4,6,7-tetrahydro-imidazo[4,5-c]pyridine-5-carboxamidine, 2-Amino-3-hydroxy-1-(2-methyl-3,4,6,7-tetrahydro-imidazo[4,5-c]pyridin-5-yl)-propan-1-one, tetrazolyl, 2-Amino-1-(2-methyl-3,4,6,7-tetrahydro-imidazo[4,5-c]pyridin-5-yl)-ethanone, 2-Methyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine, N-o-Tolyl-methanesulfonamide, 2-Methyl-benzothiazole, 3-Amino-1-(2-hydroxymethyl-pyrrolidin-1-yl)-propan-1-one, 2-Hydroxy-1-(2-hydroxymethyl-pyrrolidin-1-yl)-ethanone, 2-(2-Hydroxy-ethyl)-indan-1,3-dione, 5-Fluoro-2-methyl-1H-benzoimidazole, 2-Methyl-1H-imidazo[4,5-c]pyridine, 2-Hydroxy-N-(2-morpholin-4-yl-ethyl)-acetamide, 2-Methyl-1H-imidazo[4,5-b]pyridine, 2-Amino-1-(3-methyl-piperidin-1-yl)-ethanone, 2-Methyl-1H-benzoimidazol-4-ol, 2-Pyridin-2-yl-ethanol, N-(3-Hydroxy-propyl)-2-phenyl-acetamide, N-(3-Hydroxy-propyl)-3-phenyl-propionamide, N-(3-Hydroxy-propyl)-benzamide, N-(2-Hydroxy-ethyl)-2-phenyl-acetamide, (4-Hydroxy-butyl)-carbamic acid tert-butyl ester, (2-Hydroxy-ethyl)-carbamic acid benzyl ester, (4-Hydroxy-piperidin-1-yl)-phenyl-methanone, 4-Bromo-2-methoxy-benzylamine, 3-Methoxy-5-trifluoromethyl-benzylamine, N-(3,5-Dimethoxy-benzyl)-acetamide, 2-Methyl-1H-benzoimidazole-5-carboxamidine, and 2-Hydroxy-N-naphthalen-1-yl-acetamide.

The following structural representations further illustrate the term "het":



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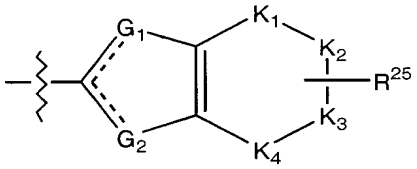

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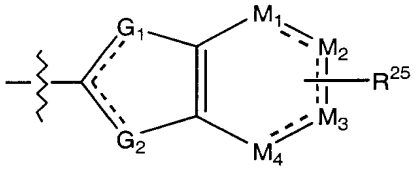

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wherein G_1 and G_2 independently at each occurance represent $S(O)_{0-2}$, NH, $N-R^{24}$, O, CR^{10}, or CHR^{10}; J_1, J_2, J_3, and J_4 independently represent CR^{10} or N, wherein at least two of J_1, J_2, J_3, and J_4 represent CH ; K_1, K_2, K_3 and K_4 independently represent $-NHR^{10}$, $-NHR^{24}$, $-CHR^{10}$, $-CH-C(=NH)-NH_2$, or $N-C(=NH)-NH_2$ wherein at least two of K_1, K_2, K_3 and K_4 represent CH_2 ; M_1, M_2, M_3 and M_4 independently represent $-NHR^{10}$, $-NHR^{24}$, $-CHR^{10}$, $-CH-C(=NH)-NH_2$, or $N-C(=NH)-NH_2$, wherein at least two of M_1, M_2, M_3 and M_4 represent CH or CH_2; and R^{25} represents H, halogen, $-C_{1-6}$ alkyl, $-NO_2$, NHR^{10}, $NH-SO_2-R^{10}$, -OH, C_{1-6} alkoxy, amidino, guanidino, $-COOR^{10}$, or $-CONHR^{10}$. The variables R^{10} and R^{24} are as defined earlier. The dashed lines indicate optional unsaturation without violating the valency rules.

The term "basic group" as used under R^7 and R^8, defined earlier, is intended to represent amidino, guanidino, $-C(=NH)N(R^{10})_2$, 2-imidazoline, -N-amidinomorpholine, N-amidino piperidine, 4-hydroxy-N-amidino piperidine, N-amidino pyrrolidine, tetrahydro pyrimidine, and thiazolidin-3-yl-methylideneamine. The compounds of the present invention were named using the "Autonom", a Beilstein Commander 2.1 Application, distributed by Beilstein.

The term "natural amino acid", as used herein is intended to represent the twenty naturally occurring amino acids in their 'L' form, which are some times also referred as 'common amino acids', a list of which can be found in *Biochemistry*, Harper & Row Publishers, Inc. (1983). The term "unnatural amino acid", as used herein, is intended to

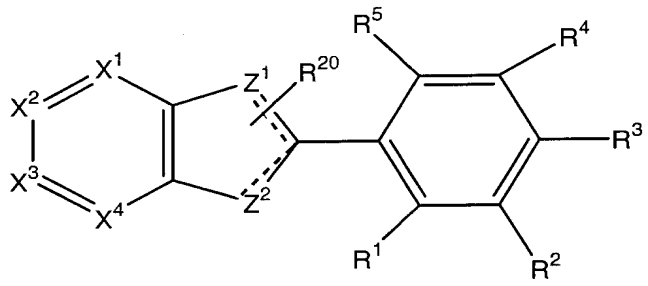
represent the 'D' form of the twenty naturally occurring amino acids described above. It is further understood that the term unnatural amino acid includes homologues of the natural amino acids, and synthetically modified form of the natural amino acids. The synthetically modified forms include amino acids having alkylene chains shortened or lengthened by up to two carbon atoms, amino acids comprising optionally substituted aryl groups, and amino acids comprised halogenated groups, preferably halogenated alkyl and aryl groups.

The term "natural amino acid side chain" is intended to represent a natural amino acid ("natural amino acid" as defined above) wherein a keto (C=O) group replaces the carboxylic acid group in the amino acid. Thus, for example, an alanine side chain is $C(=O)-CH(NH_2)-CH_3$; a valine side chain is $C(=O)-CH(NH_2)-CH(CH_3)_2$; and a cysteine side chain is $C(=O)-CH(NH_2)-CH_2-SH$. The term "unnatural amino acid side chain" is intended to represent an unnatural amino acid ("unnatural amino acid" as defined above) wherein a keto (C=O) group replaces the carboxylic acid group forming unnatural amino acid side chains similar to ones illustrated under the definition of "natural amino acid side chain" above.

It thus follows that a "N-natural amino acid side chain" substituent and "N-unnatural amino acid side chain" substituent, which can represent Q, Q^1, Q^2, Q^3, L^1, L^2, L^3 and L^4, is a group wherein the nitrogen atom (N) is the annular ring atom substituted with a natural or unnatural amino acid side chain (natural or unnatural amino acid side chain is a defined above). The point of attachment between the nitrogen atom and the natural or unnatural amino acid side chain is at the keto (C=O) group of the respective amino acids. Thus a N-natural amino acid, i.e., N-cysteine, is $N-C(=O)-CH(NH_2)-CH_2-SH$.

CLAIMS

1. A compound of Formula I:

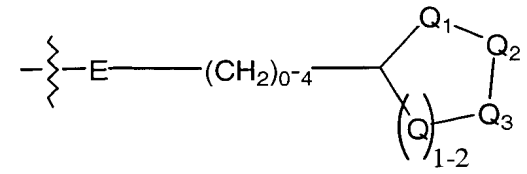


Formula I

its prodrug forms, or pharmaceutically acceptable salts thereof, wherein

R^1 represents OH, halogen, COOH, $COO-C_{1-4}$ alkyl, $O-(CH_2)_{0-1}-Ar$, $N(R^{10})_2$, CH_2OR^{10}, C_{1-6} halogenated alkyl, $O-(CH_2)_{1-4}-CO-N(R^{10})_2$, SC_{1-4} alkyl, $NHSO_2C_{1-4}$alkyl, SO_2-OH, $O-SO_2-OH$, $O-C_{1-4}$ alkyl, $O-C_{3-9}$ cyclo alkyl, $O-SO_2-O-C_{1-4}$ alkyl, $OP(O)(OH)_2$, or OPO_3C_{1-4} alkyl;

R^2, R^3, R^4, and R^5 independently at each occurance represent H, SH, OR^{10}, halogen, $COOR^{10}$, $(CH_2)_{0-6}-CONR^{11}R^{12}$, optionally substituted aryl, optionally substituted heterocyclyl, C_{4-14} cycloalkyl-C_{1-4} alkyl, C_{1-4} alkyl aryl, optionally substituted C_{1-14} straight chain, branched or cyclo alkyl, $O-(CH_2)_{2-6}-NR^{10}-(CH_2)_{0-3}-R^{24}$, $NR^{10}R^{24}$, $(CH_2)_{1-6}-NR^{33}R^{34}$, $(CH_2)_{1-6}-COOR^{33}$, $O-(CH_2)_{1-3}-CO-het$, $O-(CH_2)_{1-2}-NH-CO-aryl$, $O-(CH_2)_{1-2}-NR^{10}-CO-NR^{10}R^{33}$, $(CH_2)_{1-4}-CONR^{10}(CH_2)_{1-4}-heterocyclyl$, $O-(CH_2)_{0-2}-C(O)-NR^{33}R^{34}$, $O-(CH_2)_{1-4}-COOR^{10}$, $O-(CH_2)_{1-3}-het-R^{32}$, O-optionally substituted cycloalkyl, $O-(CH_2)_{1-4}-NR^{10}-COO-t$-butyl, $O-(CH_2)_{1-4}-NR^{10}R^{33}$, $O-(CH_2)_{1-4}-NR^{10}-C(O)-C_{0-3}$-alkyl-optionally substituted aryl, O-substituted cycloalkyl, $O-(CH_2)_{0-6}$-optionally substituted aryl, $(CH_2)_{1-4}-NH-C(O)O-(CH_2)_{1-4}-PhR^{13}R^{14}$, NO_2, $O-(CH_2)_{0-4}-C(O)-NH-$tetrahydro carboline, $NR^{10}R^{28}$, $O-(CH_2)_{1-3}$-optionally substituted het, CH_2COOCH_3, $CH=CH-COOCH_3$, 5-amidino benzimidazole, $SO_2-N(R^{10})_2$,



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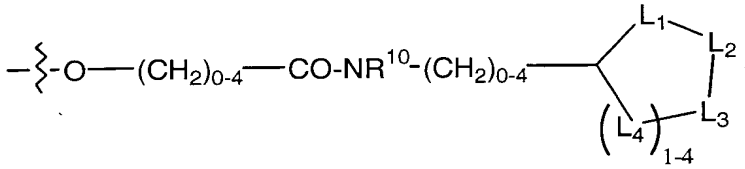

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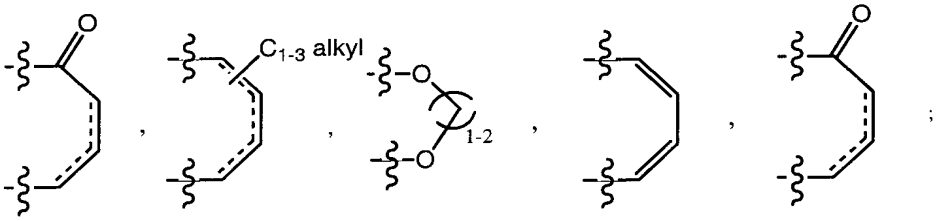
alternatively R^2 and R^3, R^3 and R^4 or R^4 and R^5 can be taken together to form



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X^1 represents C-R^6, N or N-O;
X^2 represents C-R^7, N or N-O;
X^3 represents C-R^8, N or N-O;
X^4 represents C-R^9, N or N-O;
Z^1 and Z^2 independently at each occurance represent C or N;
R^6, R^8 and R^9 independently at each occurance represents H, halogen, cyano, C_{1-4} alkyl, C_{1-4} halogenated alkyl, NO_2, O-aryl or OR^{11}, CF_3, OC_{1-4} alkyl, $(CH_2)_{0-4}$-aryl, $(CH_2)_{0-4}$-heteroaryl, or $(CH_2)_{0-4}$-heterocyclyl;
R^7 represents NH_2, NHR^{10}, $N(R^{10})_2$, $NHSO_2$-C_{1-14} alkyl, NHSO-aryl, OH, NHCO-C_{1-14} alkyl, $NHNH_2$, NHOH, NHCO-C_{1-14} alkyl, $NR^{10}NH_2$, $NHN(R^{10})_2$, $NH(C=NH)NH_2$, $NH(C=O)N(R^{10})_2$; alternatively
R^6 and R^7, R^7 and R^8, R^8 and R^9, along with the respective carbon atoms to which they are attached, can be taken together to represent a 5 to 10 atom saturated, partially saturated or aromatic, carbocyclic or heterocyclic ring structure substituted with R^{41};
R^{10} independently at each occurance represents H, $(CH_2)_{0-2}$-aryl, C_{1-4} halo alkyl, or C_{1-14} straight chain, branched or cyclo alkyl, and alternatively, when one atom is substituted with

two R^{10} groups, the atom along with the R^{10} groups can form a five to 10 cycloalkyl, heterocyclyl or aryl group;

R^{11} and R^{12} independently at each occurance represent H or C_{1-4} alkyl, $(CH_2)_{1-4}$-OH, $(CH_2)_{1-4}$-OC_{1-4}alkyl, $(CH_2)_{0-4}$-aryl, $(CH_2)_{1-4}$-$(R^{10})_2$;

R^{20} represents R^{24}, C_{1-4}-alkyl, $(CH_2)_{1-3}$-biphenyl, $(CH_2)_{1-4}$-Ph-$N(SO_2$-C_{1-2}-alkyl$)_2$, $(CH_2)_{1-4}$-NH-C(O)-R^{24}, $(CH_2)_{1-4}$-NH-SO_2-R^{24}, halogen, $COOR^{10}$, $(CH_2)_{1-4}$-Ph-$N(SO_2$-C_{1-2}alkyl), $(CH_2)_{1-4}$-NR^{10}-C(O)-R^{24}, $(CH_2)_{1-4}$-NR^{10}-SO_2-R^{24}, $(CH_2)_{1-4}$-het, $(CH_2)_{1-4}$-$CON(R^{10})_2$, $(CH_2)_{1-4}$-$N(R^{10})$-C(O)-$NR^{10}R^{24}$, $(CH_2)_{1-4}$-$N(R^{10})$-C(S)-$NR^{10}R^{24}$, or $(CH_2)_{1-3}$-COOH;

R^{24} represents R^{10}, $(CH_2)_{1-4}$-optionally substituted aryl, $(CH_2)_{0-4}OR^{10}$, CO-$(CH_2)_{1-2}$-$N(R^{10})_2$, $CO(CH_2)_{1-4}$-OR^{10}, $(CH_2)_{1-4}$-$COOR^{10}$, $(CH_2)_{0-4}$-$N(R^{10})_2$, SO_2R^{10}, COR^{10}, $CON(R^{10})_2$, $(CH_2)_{0-4}$-aryl-$COOR^{10}$, $(CH_2)_{0-4}$-aryl-$N(R^{10})_2$, or $(CH_2)_{1-4}$-het-aryl;

R^{28} represents $(CH_2)_{1-2}$-Ph-O-$(CH_2)_{0-2}$-het-R^{30}, C(O)-het, CH_2-Ph-CH_2-het-$(R^{30})_{1-3}$; $(CH_2)_{1-4}$-cyclohexyl-R^{31}, CH_2-Ph-O-Ph-$(R^{30})_{1-2}$, CH_2-(CH_2OH)-het-R^{30}, CH_2-Ph-O-cycloalkyl-R^{31}, CH_2-het-C(O)-CH_2-het-R^{30}, or CH_2-Ph-O-(CH_2)-O-het-R^{30};

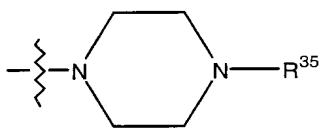
R^{30} represents $SO_2N(R^{10})_2$, H, NHOH, amidino, or $C(=NH)CH_3$;

R^{31} represents R^{30}, amino-amidino, NH-$C(=NH)CH_3$ or R^{10};

R^{32} represents H, C(O)-CH_2-NH_2, or C(O)-$CH(CH(CH_3)_2)$-NH_2;

R^{33} and R^{34} independently at each occurance represent R^{10}, $(CH_2)_{0-4}$-Ar, optionally substituted aryl, $(CH_2)_{0-4}$ optionally substituted heteroaryl, $(CH_2)_{1-4}$-CN, $(CH_2)_{1-4}$-$N(R^{10})_2$, $(CH_2)_{1-4}$-OH, $(CH_2)_{1-4}$-SO_2-$N(R^{10})_2$;

alternatively, R^{33} and R^{34} along with the nitrogen atom that they are attached to forms a 4 to 14 atom ring structure selected from tetrahydro-1H-carboline; 6,7-Dialkoxyoxy-2-substituted 1,2,3,4-tetrahydro-isoquinoline,



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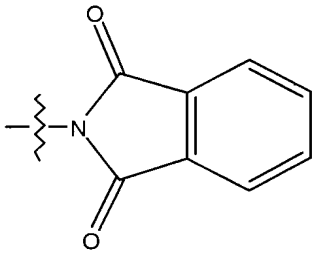
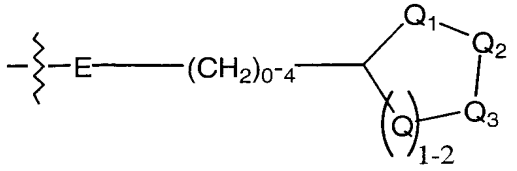


;

R^{35} represents R^{10}, SO_2-R^{10}, COR^{10}, or $CONHR^{10}$;

E represents a bond, $S(O)_{0-2}$, O or NR^{10};
Q, Q^1, Q^2, Q^3, L^1, L^2, L^3 and L^4 independently at each occurance represent N-natural or unnatural amino acid side chain, CHR^{10}, O, NH, $S(O)_{0-2}$, N-C(O)-NHR^{10}, SO_2-$N(R^{10})_2$, N-C(O)-NH-$(CH_2)_{1-4}$-R^{26}, NR^{10}, N-heteroaryl, N-C(=NH)-NHR^{10}, or N-C(=NH)C_{1-4} alkyl;
R^{26} represents OH, NH_2, or SH;
R^{41} represents NH_2, NHR^{10}, or $N(R^{10})_2$, $NHNH_2$, NHOH, $NR^{10}NH_2$, $NHN(R^{10})_2$, $NH(C=NH)NH_2$, $NH(C=O)N(R^{10})_2$;
provided that, (i) not all of X^1, X^2, X^3 and X^4 represent N or N-O simultaneously.

2. A compound of Claim 1, wherein
R^1 represents OH, halogen or COOH;
R^2, R^3, R^4, and R^5 independently at each occurance represent H, SH, OR^{10}, halogen, $COOR^{10}$, $(CH_2)_{0-4}$-$CONR^{11}R^{12}$, optionally substituted aryl, optionally substituted heterocyclyl, C_{4-14} cycloalkyl-C_{1-4} alkyl, C_{1-4} alkyl aryl, optionally substituted C_{1-14} straight chain, branched or cyclo alkyl, O-$(CH_2)_{2-6}$-NR^{10}-$(CH_2)_{0-3}$-R^{24}, $NR^{10}R^{24}$, $(CH_2)_{1-4}$-$NR^{33}R^{34}$, $(CH_2)_{1-4}$-$COOR^{33}$, O-$(CH_2)_{1-3}$-CO-het, O-$(CH_2)_{1-2}$-NH-CO-aryl, O-$(CH_2)_{1-2}$-NR^{10}-CO-$NR^{10}R^{33}$, O-$(CH_2)_{0-2}$-C(O)-$NR^{33}R^{34}$, O-$(CH_2)_{1-4}$-$COOR^{10}$, O-$(CH_2)_{1-3}$-het-R^{32}, O-optionally substituted cycloalkyl, O-$(CH_2)_{1-4}$-NR^{10}-COO-*t*-butyl, O-$(CH_2)_{1-4}$-$NR^{10}R^{33}$, O-$(CH_2)_{1-4}$-NR^{10}-C(O)-C_{0-3}-alkyl-optionally substituted aryl, O-substituted cycloalkyl, O-$(CH_2)_{0-6}$-optionally substituted aryl, $(CH_2)_{1-4}$-NH-C(O)O-$(CH_2)_{1-4}$-$PhR^{13}R^{14}$, NO_2, O-$(CH_2)_{0-4}$-C(O)-NH-tetrahydro carboline, $NR^{10}R^{28}$, O-$(CH_2)_{1-3}$-optionally substituted het, CH_2COOCH_3, CH=CH-$COOCH_3$, 5-amidino benzimidazole,



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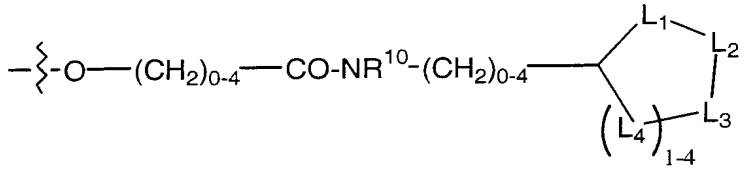
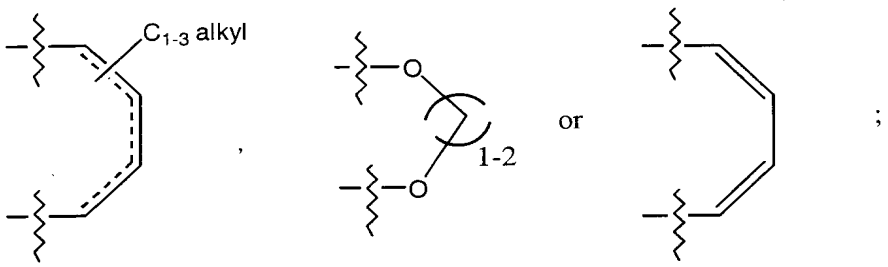


;

alternatively R^2 and R^3 taken together form



;

X^1 represents C-R^6, N or N-O;

X^2 represents C-R^7;

X^3 represents C-R^8;

X^4 represents C-R^9;

Z^1 represents C;

Z^2 represents N;

R^6, R^8 and R^9 independently at each occurance represents H, halogen, cyano, C_{1-4} alkyl, C_{1-4} halogenated alkyl, NO_2, O-aryl or OR^{11};

R^7 represents NH_2, NHR^{10}, $N(R^{10})_2$, $NHSO_2$-C_{1-14} alkyl, NHSO-aryl, OH, NHCO-C_{1-14} alkyl, $NHNH_2$, NHOH, NHCO-C_{1-14} alkyl, $NR^{10}NH_2$, $NHN(R^{10})_2$, $NH(C=NH)NH_2$, $NH(C=O)N(R^{10})_2$; alternatively

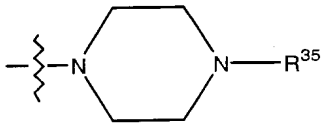
R^6 and R^7, R^7 and R^8, R^8 and R^9, along with the respective carbon atoms to which they are attached, can be taken together to represent a 6 saturated or aromatic, carbocyclic or heterocyclic ring structure substituted with R^{41};

R^{20} represents R^{24}, C_{1-4}-alkyl, $(CH_2)_{1-3}$-biphenyl, $(CH_2)_{1-4}$-Ph-$N(SO_2$-C_{1-2}-alkyl$)_2$, $(CH_2)_{1-4}$-NH-C(O)-R^{24}, $(CH_2)_{1-4}$-NH-SO_2-R^{24}, halogen, $COOR^{10}$, $(CH_2)_{1-4}$-Ph-$N(SO_2$-C_{1-2}alkyl), $(CH_2)_{1-4}$-NR^{10}-C(O)-R^{24}, $(CH_2)_{1-4}$-NR^{10}-SO_2-R^{24}, $(CH_2)_{1-4}$-het, $(CH_2)_{1-4}$-$CON(R^{10})_2$, $(CH_2)_{1-4}$-$N(R^{10})$-C(O)-$NR^{10}R^{24}$, $(CH_2)_{1-4}$-$N(R^{10})$-C(S)-$NR^{10}R^{24}$, or $(CH_2)_{1-3}$-COOH;

R^{24} represents R^{10}, $(CH_2)_{1-4}$-optionally substituted aryl, $(CH_2)_{0-4}OR^{10}$, CO-$(CH_2)_{1-2}$-$N(R^{10})_2$, $CO(CH_2)_{1-4}$-OR^{10}, $(CH_2)_{1-4}$-$COOR^{10}$, $(CH_2)_{0-4}$-$N(R^{10})_2$, SO_2R^{10}, COR^{10}, $CON(R^{10})_2$, $(CH_2)_{0-4}$-aryl-$COOR^{10}$, $(CH_2)_{0-4}$-aryl-$N(R^{10})_2$, or $(CH_2)_{1-4}$-het-aryl;

R^{28} represents $(CH_2)_{1-2}$-Ph-O-$(CH_2)_{0-2}$-het-R^{30}, C(O)-het, CH_2-Ph-CH_2-het-$(R^{30})_{1-3}$; $(CH_2)_{1-4}$-cyclohexyl-R^{31}, CH_2-Ph-O-Ph-$(R^{30})_{1-2}$, CH_2-(CH_2OH)-het-R^{30}, CH_2-Ph-O-cycloalkyl-R^{31}, CH_2-het-C(O)-CH_2-het-R^{30}, or CH_2-Ph-O-(CH_2)-O-het-R^{30};

R^{30} represents $SO_2N(R^{10})_2$, H, NHOH, amidino, or $C(=NH)CH_3$;
R^{31} represents R^{30}, amino-amidino, $NH-C(=NH)CH_3$ or R^{10};
R^{32} represents H, $C(O)-CH_2-NH_2$, or $C(O)-CH(CH(CH_3)_2)-NH_2$;
R^{33} and R^{34} independently at each occurance represent R^{10}, $(CH_2)_{0-4}$-Ar, optionally substituted aryl, $(CH_2)_{0-4}$ optionally substituted heteroaryl, $(CH_2)_{1-4}$-CN, $(CH_2)_{1-4}-N(R^{10})_2$, $(CH_2)_{1-4}$-OH, $(CH_2)_{1-4}-SO_2-N(R^{10})_2$;
alternatively, R^{33} and R^{34} along with the nitrogen atom that they are attached to forms a 4 to 14 atom ring structure selected from tetrahydro-1H-carboline; 6,7-Dialkoxyoxy-2-substituted 1,2,3,4-tetrahydro-isoquinoline,



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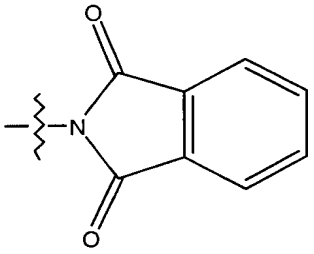


;

R^{35} represents R^{10}, SO_2-R^{10}, COR^{10}, or $CONHR^{10}$;
E represents a bond, $S(O)_{0-2}$, O or NR^{10};
W_1, W_2, W_3 and W_4 independently represent C or N; and
Q, Q^1, Q^2, Q^3, L^1, L^2, L^3 and L^4 independently at each occurance represent N-natural or unnatural amino acid side chain, CHR^{10}, O, NH, $S(O)_{0-2}$, $N-C(O)-NHR^{10}$, $SO_2-N(R^{10})_2$, $N-C(O)-NH-(CH_2)_{1-4}-R^{26}$, NR^{10}, N-heteroaryl, $N-C(=NH)-NHR^{10}$, or $N-C(=NH)C_{1-4}$ alkyl;
R^{26} represents OH, NH_2, or SH; and
provided that, (i) not all of X^1, X^2, X^3 and X^4 represent N or N-O simultaneously.

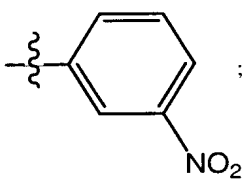
3. A compound of Claim 2 wherein
R^1 represents OH, O-Ph, COOH, or $P(O)(OH)_2$;
R^2 represents H, halo, optionally substituted alkyl or optionally substituted aryl or heteroaryl;
R^3 represents C_{0-6} alkyl-COOH;
R^5 represents H, C_{1-4} alkyl or OR^{10};
X^1 represents N or N-O;

R^7 represents NH_2 or NHC_{1-3} alkyl;
R^{20} represents H, C_{1-2} alkyl, $(CH_2)_{1-4}$-optionally substituted aryl, $(CH_2)_{1-4}$-het; $(CH_2)_{1-4}$-$N(R^{10})_2$, $(CH_2)_{1-4}$-$CON(R^{10})_2$, $(CH_2)_{1-4}$-NR^{10}-$C(O)$-R^{24}, $(CH_2)_{1-4}$-NR^{10}-SO_2-R^{24}, or $(CH_2)_{1-3}$-COOH.

4. A compound of claim 3 wherein
R^4 represents $(CH_2)_{0-6}$-$COOR^{10}$, optionally substituted heteroaryl, $(CH_2)_{0-4}$-$CONR^{10}R^{11}$, C_{1-10}-straight chain alkyl, branched alkyl or cycloalkyl group substituted with 1-3 groups selected from $COOR^{10}$, $CONHR^{10}$, OR^{10}, or aryl.

5. A compound of claim 4 wherein
R^1 represents OH or COOH.

6. A compound of claim 2 wherein
R^1 represents OH;
R^2 represents Cl, Br,



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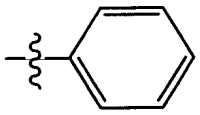
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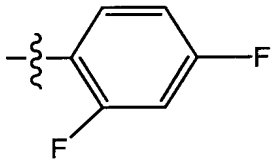

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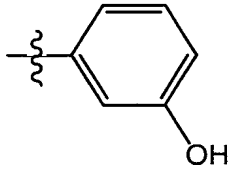

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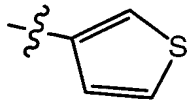

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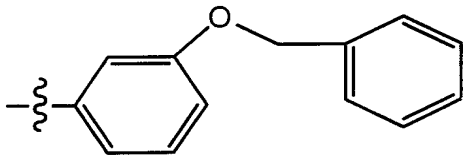

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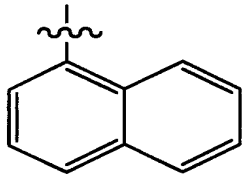
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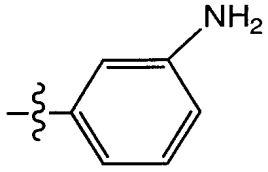

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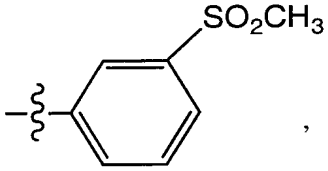

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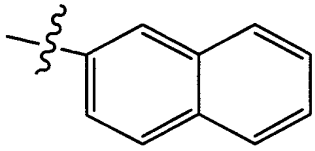
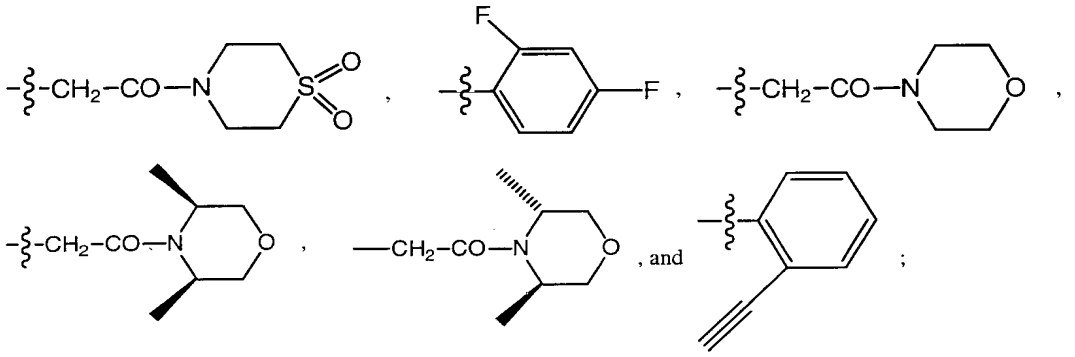

;

R^3 represents H;
R^4 represents CH_2COOH, CH_2CONH_2, CH_2COO-C_2H_5, CH_2CH_2COOH, Br, COOH, $CH_2CON(CH_2CH_2OH)_2$, $CH_2CONHCH_2CH_2OCH_3$, $CH_2CONHCH_2CH_2OCH_3$, methyl, $COOCH_3$, $CH(CH_3)COOH$, 1-tetrazolyl, SO_2NH_2, 2-carboxy-phenyl-1-y, phenyl, SO_2OH, 2-methyl-phenyl-1-yl,



R^5 represents H;
X^1 represents N;
X^2 represents CR^7;
X^3 represents CR^8;
X^4 represents CR^9;
R^7 represents NH_2;
R^8 represents methyl, chloro, H, OH or methoxy;
R^9 represents H or methyl;
Z^1 represents C;
Z^2 represents N; and
R^{20} represents benzyl, H, CH(Br)Ph, CH_2-Ph-*p*-Cl, or CH_2-pyridino.

7. A compound of claim 6 wherein
R^1 represents OH;
R^2 represents H, halogen, OH, phenyl, heteroaryl or substituted phenyl; and
R^4 represents H, halo, $(CH_2)_{0-4}$-$COOR^{10}$, $(CH_2)_{0-4}$-$CONH_2$, $(CH_2)_{0-4}$-$CONHR^{33}$, $(CH_2)_{0-4}$-heteroaryl, C_{1-8} branched alkylene-$COOR^{10}$, or C_{2-6} alkenelyne-$COOR^{10}$; and
R^{20} represents H or $(CH_2)_{0-3}$-optionally substituted phenyl, $(CH_2)_{0-3}$-aryl or $(CH_2)_{0-3}$-heteroaryl.

8. A compound of claim 2, wherein the compound is selected from
[3-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-acetic acid ethyl ester;

8-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-bromo-7-hydroxy-3,4-dihydro-2H-naphthalen-1-one;
3-[3-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-propionic acid;
[5-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-acetic acid;
[3-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-acetic acid;
2-[3-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-acetamide;
2-[3-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-N-(2-morpholin-4-yl-ethyl)-acetamide;
2-(5-Amino-1H-pyrrolo[2,3-c]pyridin-2-yl)-4,6-dichloro-phenol;
8-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-bromo-7-hydroxy-3,4-dihydro-2H-naphthalen
-1-one;
3-[3-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-propionic acid;
[5-(5-Amino-3-benzyl-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-acetic acid;
[3-(5-Amino-1H-pyrrolo[3,2-b]pyridin-2-yl)-5-chloro-4-hydroxy-phenyl]-acetic acid;
[5-(5-Amino-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-acetic acid;
2-[5-(5-Amino-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-N-(2-morpholin-
4-yl-ethyl)-acetamide;
2-[5-(5-Amino-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-N-(2-methoxy-et
hyl)-acetamide; and
2-[5-(5-Amino-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-N-(2-dimethylamino-ethyl)-acetamide.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically

effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to Claim 2 or a pharmaceutically acceptable salt thereof.

11. A method for treating or preventing a thromboembolic disorder, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to Claim 2 or a pharmaceutically acceptable salt thereof.

12. A compound of Claim 2 wherein:

X^1 represents C-R^6;
X^2 represents C-R^7;
X^3 represents N or N-O;
X^4 represents C-R^9;
Z^1 represents C; and
Z^2 represents N.

13. A compound of claim 12 wherein

R^1 represents OH, COOH, or $P(O)(OH)_2$;
R^2 represents H, halo, optionally substituted alkyl or optionally substituted aryl or heteroaryl;
R^3 represents C_{0-6} alkyl-COOH;
R^5 represents H, C_{1-4} alkyl or OR^{10};
X^1 represents N or N-O;
R^7 represents NH_2 or NHC_{1-3} alkyl;
R^{20} represents H, C_{1-2} alkyl, $(CH_2)_{1-4}$-optionally substituted aryl, $(CH_2)_{1-4}$-het; $(CH_2)_{1-4}$-$N(R^{10})_2$, $(CH_2)_{1-4}$-$CON(R^{10})_2$, $(CH_2)_{1-4}$-NR^{10}-$C(O)$-R^{24}, $(CH_2)_{1-4}$-NR^{10}-SO_2-R^{24}, or $(CH_2)_{1-3}$-COOH.

14. A compound of claim 13 wherein

R^4 represents $(CH_2)_{0-6}$-$COOR^{10}$, optionally substituted heteroaryl, $(CH_2)_{0-4}$-$CONR^{10}R^{11}$, C_{1-10}-straight chain alkyl, branched alkyl or cycloalkyl group substituted with 1-3 groups selected from $COOR^{10}$, $CONHR^{10}$, or OR^{10}.

15. A compound of claim 14 wherein
R^1 represents OH or COOH.

16. A compound of claim 22 wherein
R^7 represents NH_2.

17. A compound of claim 16 wherein
R^1 represents OH;
R^2 represents H, halogen, OH, phenyl heteroaryl, or substituted phenyl; and
R^4 represents H, halo, $(CH_2)_{0-4}$-$COOR^{10}$, $(CH_2)_{0-4}$-$CONH_2$, $(CH_2)_{0-4}$-$CONHR^{33}$, $(CH_2)_{0-4}$-heteroaryl, C_{1-8} branched alkylene-$COOR^{10}$, or C_{2-6} alkenyl-$COOR^{10}$; and
R^{20} represents H or (CH_2)1-3-optionally substituted phenyl.

18. A compound of claim 12, wherein the compound is selected from
2-(5-Amino-1H-pyrrolo[2,3-c]pyridin-2-yl)-4,6-dichloro-phenol; and
2-(5-Amino-3-benzyl-1H-pyrrolo[2,3-c]pyridin-2-yl)-4,6-dichloro-phenol.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to Claim 12 or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to Claim 12 or a pharmaceutically acceptable salt thereof.

21. A method for treating or preventing a thromboembolic disorder, comprising administering t a patient in need thereof a therapeutically effective amount of a compound according to Claim 12 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Int ıtional Application No
PCT/US 01/08839

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 C07D209/08 C07D209/12 C07D487/04 A61K31/437
A61K31/519 A61P7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 576 343 A (NAGAHARA TAKAYASU ET AL) 19 November 1996 (1996-11-19) cited in the application the whole document	1,9-11, 19-21
A	WO 99 26941 A (AXYS PHARM INC) 3 June 1999 (1999-06-03) claims 1,6-8; examples	1,9-11, 19-21

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 August 2001	05/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bosma, P

INTERNATIONAL SEARCH REPORT

International application No.
PCT/ US/ 01/08839

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

SEE ANNEXE

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 9-11,19-21

Present claim 1 relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds as prepared in the examples and compounds of Formula I, in which only one of Z1 and Z2 represents a nitrogen atom, and the number of nitrogens atoms in the ring with X1, X2, X3, and X4 has a maximum of 2. Also the pharmaceutical use claims 9-11 and 19-21 have been restricted to the above indicated limited scope of the claimed subject-matter.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ational Application No
PCT/US 01/08839

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